Determining the Role of Synthetic Cannabinoids in Eye Pressure And Tolerability Measurements (DREAM)

A Pilot, Randomised, Cross-Over Study to Determine the Effects of an Oral, Peripherally Selective, Synthetic Cannabinoid ART27.13 on Intraocular Pressure

Protocol Number	24077AAB-UC
Protocol Version	V4.0 Final
Protocol Date	20/05/2026
Protocol Amendment Number	3
ISRCTN	10996483
Ethics Reference Number	25/NE/0218
Sources of Monetary or Material Support	
Funder	Glaucoma UK Public Health Agency (PHA), Health and Social Care (HSC) Research & Development Division, Northern Ireland
Sponsor Details	
Sponsor	Belfast Health and Social Care Trust The Royal Hospitals Grosvenor Road Belfast, BT12 6BA Northern Ireland
Chief Investigator	Professor Augusto Azuara-Blanco Centre for Public Health, ICS-A Queen's University Belfast Grosvenor Road Belfast, BT12 6BA Northern Ireland

PROTOCOL AUTHORISATION

Protocol Title	A Pilot, Randomised, Cross-Over Study to Determine the Effects of an Oral, Peripherally Selective, Synthetic Cannabinoid ART27.13 on Intraocular Pressure
Protocol Acronym (if applicable)	DREAM
Protocol Number	24077AAB-UC
Protocol Version Number/Date	V4.0 Final_20/05/2026

A review of the protocol has been completed and is understood and approved by the following:

_____	_____	_____ / _____ / _____
Chief Investigator	Signature	Date
_____	_____	_____ / _____ / _____
Statistician	Signature	Date

PROTOCOL AMENDMENT HISTORY

Amendment No.	Version	Date	Summary of Key Changes
1	2	19Dec2025	The following sections have been updated: Section 1 exclusion criteria Section 7.3.1 inclusion criteria Section 7.3.2 exclusion criteria Section 8.1 Screening procedure Section 8.4 General Practitioner Contact 10.10 Study Drug Termination Criteria 10.11 Rescue Treatment and Concomitant Care 11.1 Participant Assessments 14.10 Pregnancy Reporting 19.1 Appendix 1
2	3		Section 1 exclusion criteria Section 6.2 Study Schematic Diagram Section 7.3.2 exclusion criteria Section 10.10 Study Drug Termination Criteria Section 11.1 Participant Assessments Section 13.2.2 Statistical Methods Section 14.8 Suspected Unexpected Serious Adverse Reaction (SUSAR) Section 14.9 Recording and Reporting Urgent Safety Measures
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LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
AEA	Anandamide
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BHSCT	Belfast Health and Social Care Trust
BP	Blood Pressure
CAReS	Cancer Appetite Recovery Study
CB_1	Cannabinoid Receptor Type 1
CB_2	Cannabinoid Receptor Type 2
CBD	Cannabidiol
CI	Chief Investigator
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
GAT	Goldmann Applanation Tonometry
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GP	General Practitioner
HAP	Human Abuse Potential
HDPE	High Density Poly Ethylene
HRA	Health Research Authority
HSC	Health and Social Care
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LFT	Liver Function Test
MHRA	Medicine and Healthcare Products Regulatory Agency
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NHS	National Health Service
NICRF	Northern Ireland Clinical Research Facility
NICTU	Northern Ireland Clinical Trials Unit
PgP	P-glycoprotein
PHA	Public Health Agency

PI	Principal Investigator
PPI	Patient and Public Involvement
RGCs	Retinal Ganglion Cells
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
U&E	Urea and Electrolyte
ULN	Upper Limit of Normal
VAMS	Visual Analog Mood Scale
VAS	Visual Analog Scale
VF	Visual Fields
Δ-9-THC	Delta-9-tetrahydrocannabinol

1 STUDY SUMMARY

Scientific title	A Pilot, Randomised, Cross-Over Study to Determine the Effects of an Oral, Peripherally Selective, Synthetic Cannabinoid ART27.13 on Intraocular Pressure
Public title	Determining the Role of Synthetic Cannabinoids in Eye Pressure And Tolerability Measurements (DREAM)
Health condition(s) or problem(s) studied	Glaucoma
Study Design	A pilot, randomised, double-masked, placebo-controlled, single site, cross-over trial
Study Aim and Objectives	**Aim** The study aims to assess the preliminary efficacy and safety of a peripherally selective, synthetic cannabinoid (ART27.13), given orally, to reduce intraocular pressure (IOP) in patients with ocular hypertension or early primary open angle glaucoma. **Objectives** 1. To evaluate the IOP lowering efficacy of ART27.13 2. To assess the safety and tolerability of ART27.13
Study Intervention and Comparator	Intervention: Oral, peripherally selective, synthetic cannabinoid, ART27.13 Comparator: Placebo
Primary Outcome	Intraocular pressure (IOP) after 3 weeks of use of ART27.13 or Placebo IOP will be measured with Goldmann Applanation Tonometry (GAT).
Secondary Outcomes	1. Safety as defined by the incidence of Adverse Events (AEs)/Serious Adverse Events (SAEs) 2. Tolerability of ART27.13 in relation to effect on mood 3. The abuse potential of ART27.13
Inclusion and Exclusion Criteria	**Inclusion criteria** 1. Age ≥ 40 years for males, ≥ 55 years for females 2. Ocular hypertension or early primary open angle glaucoma (visual field loss, less severe than - 6 dB in a standard 24-2 Humphrey visual field test)

	3. IOP between 20 and 35 mmHg inclusive* *The patient's IOP at randomisation must fall between 20 and 35 mmHg inclusive, in either an untreated or washed-out state. **Exclusion criteria** 1. Any other clinically significant ocular disease in either eye 2. Current liver disease or laboratory results with elevated levels of liver transaminases (AST or ALT >3 x upper limit of normal (ULN) at screening visit) 3. Renal failure (eGFR <30 mL/min/1.73m² at screening visit) 4. Heart disease (e.g. myocardial infarction or arrhythmia) 5. Diagnosed with cancer in the last 12 months (with exception of non-melanoma skin cancer) 6. Prior ocular laser treatment within previous 12 months of enrolment 7. Prior surgical treatment for glaucoma 8. Intraocular surgery within previous 12 months of enrolment 9. Use of cannabinoids for other purposes within 3 months of enrolment (with the exception of cannabidiol (CBD)) 10. Woman of childbearing potential i.e has had a menstrual cycle in the last 12 months or has not been permanently sterilised. 11. Male participants with sexual partners who have not agreed to use a condom during treatment and for 1 month after the last dose is administered. 12. Current use of systemic beta-blockers 13. Within 4 weeks prior to enrolment been on or expected to be on medications that are known to be strong cytochrome P450 CYP3A4 inhibitors or inducers 14. Within 4 weeks prior to enrolment been on or expected to be on medications that are known to be P-glycoprotein (PgP) Inhibitors or Substrates 15. Any clinical condition that, in the investigator's opinion, would make the participant unsuitable for the trial 16. Non-English speaking patients or those who do not adequately understand verbal or written information 17. Any known allergy to the active ingredient or excipients

	18. History of any recreational or illicit drug use, alcohol misuse, or other drug misuse within the last 24 months. 19. Any history of depression in the last five years or current use of anti-depressant medication. 20. Not agreed to abstain from driving or operating heavy machinery for the first 4 weeks of each treatment cycle or longer if AEs warrant. 21. Total serum Bilirubin > 1.5 x upper limit of normal 22. Any history of suicidal behaviour or serious suicidal ideation, defined as Category 4 or greater on the Columbia Suicide Severity Rating Scale (C-SSRS) at screening. 23. Declined consent
Countries of Recruitment	Northern Ireland, UK
Study Setting	Hospital Eye Services
Target Sample Size	10 completed participants
Study Duration	18 months

2 STUDY TEAM

Chief Investigator	**Professor Augusto Azuara-Blanco** Centre for Public Health, ICS-A Queen's University Belfast Grosvenor Road Belfast, BT9 7BL Northern Ireland Email: a.azuara-blanco@qub.ac.uk
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3 ROLES AND RESPONSIBILITIES

3.1 Funder

The study is funded by Glaucoma UK and the Public Health Agency (PHA), Health and Social Care (HSC) Research & Development Division, Northern Ireland. The views expressed are those of the author(s) and not necessarily those of Glaucoma UK or the PHA, HSC Research & Development Division. The funders will have no role in the study design, data acquisition, analysis and interpretation, or manuscript preparation.

3.2 Sponsor

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation undertaking Sponsor delegated duties in relation to the management of the study. The Sponsor will have no role in the collection, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication.

3.3 Trial Oversight Committees

3.3.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. It will comprise the CI, representatives from the Clinical Trials Unit (CTU), and any other co-investigators who provide trial specific expertise as required at the time. The TMG will meet face to face or by teleconference on a monthly basis, and will communicate between times via telephone and email as needed. The roles and responsibilities of the TMG will be detailed in the TMG Charter. Meetings will be formally minuted and stored in the Trial Master File (TMF).

3.3.2 Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be convened, comprising two independent clinicians with experience in undertaking clinical trials, an independent statistician and a patient representative. The DMEC's overarching responsibility is to safeguard the interests of trial participants, in particular with regards to safety, and assist and advise the CI and TMG so as to protect the validity and credibility of the trial. The membership, the role of the DMEC and the frequency of meetings will be listed in the DMEC Charter. Representatives of the Sponsor, Funder and the NICTU may attend the open session of DMEC meetings. The DMEC will make recommendations to the TMG and Sponsor on whether there are any ethical, safety, or other reasons why the trial should not continue. Meetings will be formally minuted and stored in the TMF. Following recommendations from the DMEC, the TMG will decide what actions, if any, are required. It will be the responsibility of the TMG to inform the Sponsor if concerns exist about participant safety, following which the Sponsor will take appropriate action.

3.3.3 User Involvement

The study was reviewed by patient and public involvement (PPI) representatives as part of the grant application and funding awarded by Glaucoma UK. An independent patient representative will sit on the DMEC to ensure appropriate representation of, and sensitivity to, the views of patients. They will also actively contribute to the design and content of all patient-facing materials throughout the course of the study.

4 BACKGROUND AND RATIONALE

4.1 Background Information

Glaucoma is a leading cause of irreversible blindness. The term 'glaucoma' refers to a group of heterogenous pathologies that result in excavation of the eye, progressive damage to the retinal ganglion cells (RGCs), optic nerve damage, and subsequent visual impairment. There are currently no treatments that cure glaucoma; however, medications that attenuate intraocular pressure (IOP) may slow or prevent disease progression. Whilst elevated IOP is fundamental in glaucoma pathology, several other factors that contribute to the disease include aberrant ocular blood flow, low intracranial pressure, mitochondrial dysfunction, autoimmunity, and abnormal structural integrity of the lamina cribrosa.

It is estimated that around 80 million people currently suffer from glaucoma (Quigley and Broman, 2006) [1]. By 2040, this number is expected to increase to >111 million (Tham et al., 2014) [2]. Tham et al. (2014) also showed that the global prevalence for individuals aged between 40-80 years was 3.54%. Regarding primary open-angle glaucoma, men had higher prevalence rates than women, those of African descent were more susceptible than Europeans, as were those living in urban areas compared to those living in rural areas (Tham et al., 2014) [2]. Glaucoma is associated with several risk factors. These include genetics (Wang et al., 2019) [3], age and smoking status (Niven et al., 2019) [4], hypercholesterolaemia (Posch-Pertl et al., 2022) [5], and high IOP (Weinreb et al., 2014) [6].

Current medications aim to reduce IOP. This can be achieved through increased aqueous humour outflow, reduced aqueous humour production, or reduced episcleral venous pressure. Drugs that are commonly used to treat glaucoma include prostaglandin F2α analogues, Rho kinase inhibitors, β-blockers, α2-agonists, carbonic anhydrase inhibitors, and cholinergic agonists. A meta-analysis determined that over 50% of glaucoma patients require two or more drugs to successfully reduce IOP (Tanna et al., 2010) [7]. This mercurial efficacy also coincides with several side-effects associated with each class of drugs. Aside from medications, surgeries may also reduce IOP through enhancement of aqueous humour outflow (e.g., laser trabeculoplasty, laser peripheral iridotomy, and incisional glaucoma tube shunt surgery). Despite this, not all surgeries are successful, and some may only modestly reduce IOP, with some patients requiring additional treatment after surgery (Lavia et al., 2017; Napier and Azuara-Blanco, 2018) [8, 9]. Glaucoma surgeries may also increase the risk of intraocular infections (Gedde et al., 2001; Kangas et al., 1997) [10, 11].

Multiple clinical studies have been conducted evaluating derivatives and/or combinations of approved glaucoma therapeutic agents, i.e., prostaglandin analogues, beta-blockers, and rho kinase inhibitors. This includes evaluation of combinations of prostaglandin analogues and beta-blockers, as well as slow-release or preservative-free versions of prostaglandin analogues. The Medical University of Vienna completed a phase 2 clinical trial which assessed the effect of dronabinol (a synthetic delta-9-tetrahydrocannabinol [Δ-9-THC]; 5 & 10 mg) on ocular haemodynamics in patients with primary open angle glaucoma (Hommer et al., 2020) [12].

Additional clinical studies have been conducted to assess the effectiveness of phytocannabinoids or synthetic cannabinoids on glaucoma. When given orally, Δ-9-THC shows a robust reduction of IOP 30 mins to 3 hrs after administration (Flach, 2002; Hepler and Petrus, 1976; Hepler et al., 1976; Tomida et al., 2006) [13, 14, 15, 16]. However, Flach (2002) reported that 8 out of 9 patients discontinued their 9-month Δ-9-THC treatment programme within 8–20 weeks due to tolerance and toxicity-related phenomena. Tomida et al. (2006) [16] found that whilst Δ-9-THC acutely reduced IOP, its effect was short-lasting. Tomida et al. (2006) [16] also showed that cannabidiol (CBD) did not reduce IOP, but transiently increased IOP at a higher dose. Tiedeman et al. (1981) [17] assessed synthetic Δ-1-THC cannabinoids, BW146Y and BW29Y. The authors found that oral administration of BW29Y had no

effect on IOP, whilst BW146Y dose-dependently reduced IOP after 1-hour post-administration. Dronabinol and nabilone (synthetic versions of Δ-9-THC) significantly reduce IOP after 2 hours (Newell et al., 1979; Plange et al., 2007) [18, 19]. Oral-dosing of palmitoylethanolamide has also been shown to reduce IOP in clinical studies (Costagliola et al., 2014; Gagliano et al., 2011; Pescosolido et al., 2011; Rossi et al., 2020; Strobbe et al., 2013) [20, 21, 22, 23, 24].

Clinical studies have used inhaled cannabis products to assess their effect on glaucoma. When inhaled, cannabis products or cigarettes containing Δ-9-THC can significantly reduce IOP within 30-80 mins (Flom et al., 1975; Hepler and Frank, 1971; Hepler and Petrus, 1976; Hepler et al., 1976; Merritt et al., 1980) [14, 15, 25, 26, 27], lasting up to 4 hours post-administration (Hepler and Petrus, 1976) [14]. However, Hepler and Frank (1971) [26] reported that IOP reverted to baseline within a few hours. Flom et al. (1975) [25] found that inhaled Δ-9-THC reduced IOP 80 mins after administration, but this effect was not significant at any later time-points. Merritt et al. (1980) [27] found that Δ-9-THC reduced blood pressure along with IOP and that glaucoma patients with hypertension experienced the greatest reduction in IOP. This suggests that reductions in IOP following Δ-9-THC inhalation may be in part due to a hypotensive effect.

Clinical studies have also assessed the use of topical cannabinoids in the form of eye drops. Several studies have shown no acute or chronic effect of topical Δ-9-THC (Green and Roth, 1982; Jay and Green, 1983; Merritt et al., 1981 a, b) [28, 29, 30, 31]. Using a synthetic cannabinoid, Porcella et al. (2001) [32] found that topical application of WIN 55,212-2 reduced IOP 1 hour after administration; however, this effect began to wear off after 2 hours. Pescosolido et al. (2018) showed that long-term treatment with Bediol (Δ-9-THC and CBD) or Bedrocan (Δ-9-THC and CBD) had no effect on 4 out of 5 glaucoma patients, whilst 1 intractable uveitic glaucoma patient showed a reduction in IOP with Bedrocan use [33]. One potentially limiting factor of topical cannabinoid use is the choice of vehicle. Cannabinoids are lipophilic and require an oil-based solution to dissolve. Most clinical studies have used light mineral oil to deliver topical cannabinoids; however, this raises issues of water-insolubility and penetration of the cornea. Interestingly, Porcella et al. (2001) combined WIN 55,212-2 with 2-hydroxypropyl-β-cyclodextrin meaning they were able to dilute the drug in a saline solution [33]. A Jamaican eye drop called Canasol has been commercially available since the 1990s (West and Homi, 1996)[34]. Despite claiming to reduce IOP, its efficacy and safety have not been scientifically verified.

Finally, intravenous administration of cannabinoids can reduce IOP significantly within 30 minutes (Cooler and Gregg, 1977; Purnell and Gregg, 1975) [35, 36]. However, these effects are short-lived (dissipating within a few hours) and were associated with side-effects including nausea, confusion, euphoria, and dizziness (Purnell and Gregg, 1975) [36].

Whilst systemically delivered cannabinoids can reduce IOP in clinical cohorts, their therapeutic effect appears to be short-lived and may also coincide with toxicity-related phenomena when administered via inhalation or injection. Topical cannabinoid products show poor efficacy when administered topically. This may be related to the oil-based vehicle typically used to administer the drugs, which may hinder intraocular penetration. Considering these issues, it has been suggested that cannabinoids may be more effective as adjunct therapies for current hypotensive drugs, particularly as an oral tablet formulation given the issues seen with both inhaled and topical methods (Afflitto et al., 2022; Hudson et al., 2011) [37, 38].

The mechanisms by which cannabinoids reduce IOP are as follows. Cannabinoid receptor type 1 (CB_1) is expressed throughout the eye, namely in the retina, iris, Schlemms' canal, and ciliary muscle (see Afflitto et al., 2022) [37]. Preclinical research suggests that activation of CB_1 increases and decreases aqueous humour outflow and inflow, respectively, whilst CB_2 activation increases aqueous humour outflow. These findings have been shown in *in vivo* models (e.g., mice, rats, dogs, rabbit, and monkeys) with topical, oral, or intravenous administration, as well as in porcine anterior segment perfused organ

culture models (see Afflitto et al., 2022) [33]. Anandamide (AEA, the first identified endogenous cannabinoid compound) and CP 55,940 (synthetic CB_1 agonist) regulate bovine ciliary muscle contraction to reduce IOP (Romano et al., 2004) [39]. This CB_1R-mediated regulation of the ciliary muscle may also affect vasodilation and subsequently suppress further generation of aqueous humour (Su et al., 2015) [40]. Trans-Δ-9-THC (isomer) and cannabigerol (a phytocannabinoid that activates CB_1) increase outflow of aqueous humour via dilation of Sclemm's canal (Colasanti, 1990) [41]. AEA and Δ-9-THC increase cyclooxygenase-2 activity, which in turn enhances expression of prostaglandins and metalloproteinases that may contribute to a reduction in IOP (Rösch et al., 2006) [42]. A recent *in vitro* and *in vivo* study found cannabinol (a phytocannabinoid that activates CB_1) to be neuroprotective and efficacious in IOP reduction (Somvanshi et al., 2022) [43].

Drugs that are currently used to treat glaucoma may reduce IOP in some patients. However, IOP is only one factor in the pathogenesis of glaucoma. Glaucoma is also characterised by degeneration of the retinal ganglion cells (RGCs) and optic nerve damage. Currently used drug classes are not known to be neuroprotective, i.e., they may reduce IOP, but they have no protective effect on RGCs nor do they attenuate optic nerve damage (Zhang et al., 2012)[44]. Whilst cannabinoids can reduce IOP, they also have anti-oxidative and anti-inflammatory effects (Klein et al., 1998; Marsicano et al., 2002) [45, 46]. Cannabinoids are thought to protect RGCs via inhibition of glutamate (excitatory neurotransmitter), endothelin-1 (vasoconstrictor), and nitric oxide (oxidative stress mediator), which are compounds known to be involved in the pathology of glaucoma (Samy et al., 1994) [47]. For example, long-term administration of Δ-9-THC in rats reduces IOP and attenuates RGC cell death by up to 75% (Schwitzer et al., 2015) [48]. Δ-9-THC-mediated inhibition of endothelin-1 in humans facilitates adaptive blood perfusion of the optic nerve whilst also increasing retinal perfusion (Green et al., 1978; Hommer et al., 2020) [49,50]. AEA-mediated activation of retinal and central CB_1 and CB_2 receptors protects RGCs via inhibition of nitric oxide and inflammatory cytokines associated with oxidative stress (Krishnan & Chatterjee, 2015) [51].

In this study an oral dose of 600 µg of ART27.13, a synthetic, peripherally selective cannabinoid, will be used. ART27.13 is an investigational drug under development by Artelo Biosciences. Despite being a cannabinoid agonist, ART27.13 is not considered a controlled substance in multiple regions including the UK, Ireland, Norway and Australia. This medication has both CB_1 and CB_2 agonist properties, with the potential capability to generate CB_1 (reducing IOP) and CB_2 (neuroprotective) -mediated positive effects in patients with glaucoma. ART27.13 has been studied in multiple human trials. Further details on ART27.13 can be found in the current version of the Investigator's Brochure (IB). From 2007 to 2008, ART27.13 was evaluated in five Phase 1 clinical trials on 325 subjects. ART27.13 was administered orally in 205 subjects with dose ranging from 10 to 1600 µg and its safety, tolerability, and pharmacokinetics were investigated. These studies are summarized in Table 1 below.

Additionally, an ART27.13 clinical study currently underway (ART27.13-100), "A Phase 1/2 Trial of the Synthetic Cannabinoid ART27.13 in Patients with Cancer Anorexia and Weight Loss" (https://www.isrctn.com/ISRCTN15607817), evaluated the safety of doses of 150, 250, 400, and 650 µg/day for 13 weeks in the initial (Stage 1) portion of the study. Based on these findings, which demonstrated ART27.13 was safe and well tolerated at all doses evaluated, a starting dose of 650 µg/day is being evaluated for efficacy in Stage 2 of the study.

Table 1. Phase 1 Clinical Trials of ART27.13

Acronym (n=total/drug)	Full Title	Indication	Design	Schedule	Dose (Number of Subjects)
SAD1 (56/42)	A Phase I, First Time in Man, Single-Centre, Randomised, Double-Blind (within panels), Placebo-Controlled Study to Investigate Safety, Tolerability and Pharmacokinetics of AZD1940 (ART27.13) after Administration of Oral Single Ascending Doses in Healthy Volunteers	Healthy Volunteers	Parallel	Single dose oral solution	10 µg fast (6) 40 µg fast (6) 125 µg fast (6) 400 µg fast (6) 800 µg fast (6) 1600 µg fast (6) 800 µg fed (6) Placebo (14)
J-SAD (24/18)	A Phase I, Single-Centre, Randomised, Double-Blind (within panels), Placebo-Controlled Study to Investigate Safety, Tolerability and Pharmacokinetics of AZD1940 (ART27.13) after Administration of Oral Single Ascending Doses in Japanese Healthy Male Volunteers	Healthy Volunteers	Parallel	Single dose oral solution	125 µg (6) 400 µg (6) 600 µg (6) Placebo (6)
POP 1 study (44/44)	A Phase I, Single-Centre, Randomised, Double-Blind, Placebo-Controlled Crossover Study in Healthy Volunteers to Evaluate Effects of a Single Oral Dose of AZD1940 (ART27.13) on Intradermal and Topical Capsaicin-evoked Pain Symptoms	Healthy Volunteers/ Capsaicin	Crossover	Single dose oral solution	400 µg/Placebo (22) 800 µg/Placebo (22)
POP 2 study (151/61	A Randomised, Double Blind, Placebo-Controlled Study to Investigate the Analgesic Efficacy of a Single Dose of AZD1940 (ART27.13), in Patients Undergoing Impacted Mandibular Third Molar Extraction	Molar Extraction	Parallel	Single dose oral solution	800 µg (61) Placebo (59) Naproxen (31)
MAD (50/40)	A Phase I, Multi-Centre, Randomised, Double-blind, Placebo-controlled Study to Investigate the Safety, Tolerability and Pharmacokinetics of AZD1940 (ART27.13), Including an Interaction Study, After Administration of Oral Multiple Ascending Doses in Adult Subjects with Chronic Low Back Pain	Low Back Pain	Parallel	Once a day for 12 days oral solution	130 µg (8) 250 µg (8) 400 µg (8) 650 µg (8) 1000 µg (8) Placebo (10)

4.2 Rationale for the Study

Evidence suggests that cannabinoids effectively reduce IOP; however, their central side effects are often difficult to tolerate. Clinical studies in glaucoma show that many patients discontinue cannabinoids due to these psychiatric effects. ART27.13 is a peripherally selective cannabinoid which targets CB_1 and CB_2 receptors, but with minimal brain penetration, thus with the potential to mitigate these side effects. Additionally, preclinical research shows that ART27.13 does accumulate in rabbits' uvea and retinal pigment epithelia, which are areas of interest for glaucoma. Thus, we hypothesise that ART27.13 will decrease IOP in glaucoma with minimal central nervous system (CNS) side effects. Previous clinical studies with ART27.13 have shown that it is safe and well-tolerated, and may provide an alternative to currently licenced glaucoma medications.

All licenced medications for glaucoma come as eye drops. Research shows that patient compliance to eye drops is poor, and that an oral dosage form may be preferred (Zaharia et al, 2022) [52]. Once daily oral dosing of ART27.13 may offer a more optimised mode of administration that is agreeable with patients. This would enhance compliance rates, with a greater benefit to the patient when compared with other dosage forms.

Overall, there is an unmet need in the treatment of glaucoma in patients. Currently licenced medications are often co-administered and come in a difficult to use dosage form. A trial with ART27.13 is required to investigate whether a safe, easily consumed alternative can be made available to the glaucoma population.

4.3 Rationale for the Intervention / Comparator

The study is to be conducted in patients over the age of 40 with ocular hypertension or early primary open angle glaucoma. Primary open angle glaucoma was chosen as it is the most prevalent type of glaucoma. The dose for the study, (600 µg once daily) is based on previous clinical trials experience, where doses of up to 1600 µg have been shown to be safe and well tolerated. (Table 1).

An ongoing Phase1/2 trial, ART27.13-100 (CAReS), of a peripherally selective CB1/CB2 receptor agonist, is currently underway in patients with cancer and anorexia. Stage 1 is complete with doses up to 650 µg deemed safe and tolerated. Twenty-seven patients received at least one dose of ART27.13 in Stage 1. There were no events considered as dose limiting toxicities (DLTs) and no fatal AEs related to trial treatment. The most common (> 1 patient) AEs related to trial drug were somnolence (11%) and dry mouth (11%). No dose response for AEs was noted. Based on the positive safety profile and the response pattern observed, a dose of 650 µg was deemed to be a safe and potentially effective, starting dose for the placebo-controlled part of the trial. Stage 2 is recruiting with patients able to escalate from 650 µg through 1000 µg to 1300 µg at monthly intervals should the study investigator deem that to be safe. Maximum duration of dosing is three months for each patient. As of 27 July 2025, there have been no medically significant differences observed in the AE profile in Stage 2 to that observed in Stage 1. Four patients have escalated through 650 µg after one month dosing to 1000 µg with no further dose escalation and eight patients have received 650 µg for one month, 1000 µg for one month and escalated to the maximum allowable dose per protocol, of 1300 µg for the final month of treatment. Pharmacokinetic analysis of ART27.13 shows that it can take between 2 and 4 weeks to reach a steady exposure state in the plasma. There was no significant increase in the exposure between the 2 and 4 week time points, therefore the length of the intervention in the proposed study is 3 weeks which allows for the drug to reach this steady state level.

All participants on topical glaucoma treatment will undergo a four-week wash out period before baseline and will not use any glaucoma drops during the trial. The study will run as a crossover design in which one half of the recruited participants will be randomised to receive ART27.13 or placebo for three weeks. Following this, patients who initially received ART27.13 will then be switched to placebo for three weeks (and vice versa) following a three-week washout period. This design was chosen to maximise the efficiency of the study, ensuring that data on ART27.13 is acquired from all study participants. The placebo will be in capsule form, identical in appearance to ART27.13, to minimise the risk of bias.

5 STUDY AIM, OBJECTIVES AND OUTCOMES

5.1 Research Hypothesis

Our hypothesis is that a peripherally selective synthetic CB_1/CB_2 agonist (ART27.13) will reduce glaucoma patient's IOP compared with placebo.

5.2 Study Aim

The study aims to assess the efficacy and safety of a peripherally selective synthetic cannabinoid (ART27.13), given orally, to reduce IOP in patients with ocular hypertension or early primary open angle glaucoma.

5.3 Study Objectives

1. To evaluate the IOP lowering efficacy of ART27.13
2. To assess the safety and tolerability of ART27.13

5.4 Primary Outcome

The primary outcome is intraocular pressure (IOP) after 3 weeks of use of ART27.13 or placebo. IOP will be measured with Goldmann Applanation Tonometry (GAT).

5.5 Secondary Outcomes

1. Safety as defined by the incidence of Adverse Events (AEs)/Serious Adverse Events (SAEs)
2. Tolerability of ART27.13 in relation to effect on mood
3. The abuse potential of ART27.13

The tolerability and abuse potential of ART27.13 will be determined through the use of two visual analogue scale (VAS) questionnaires that will be completed throughout the trial.

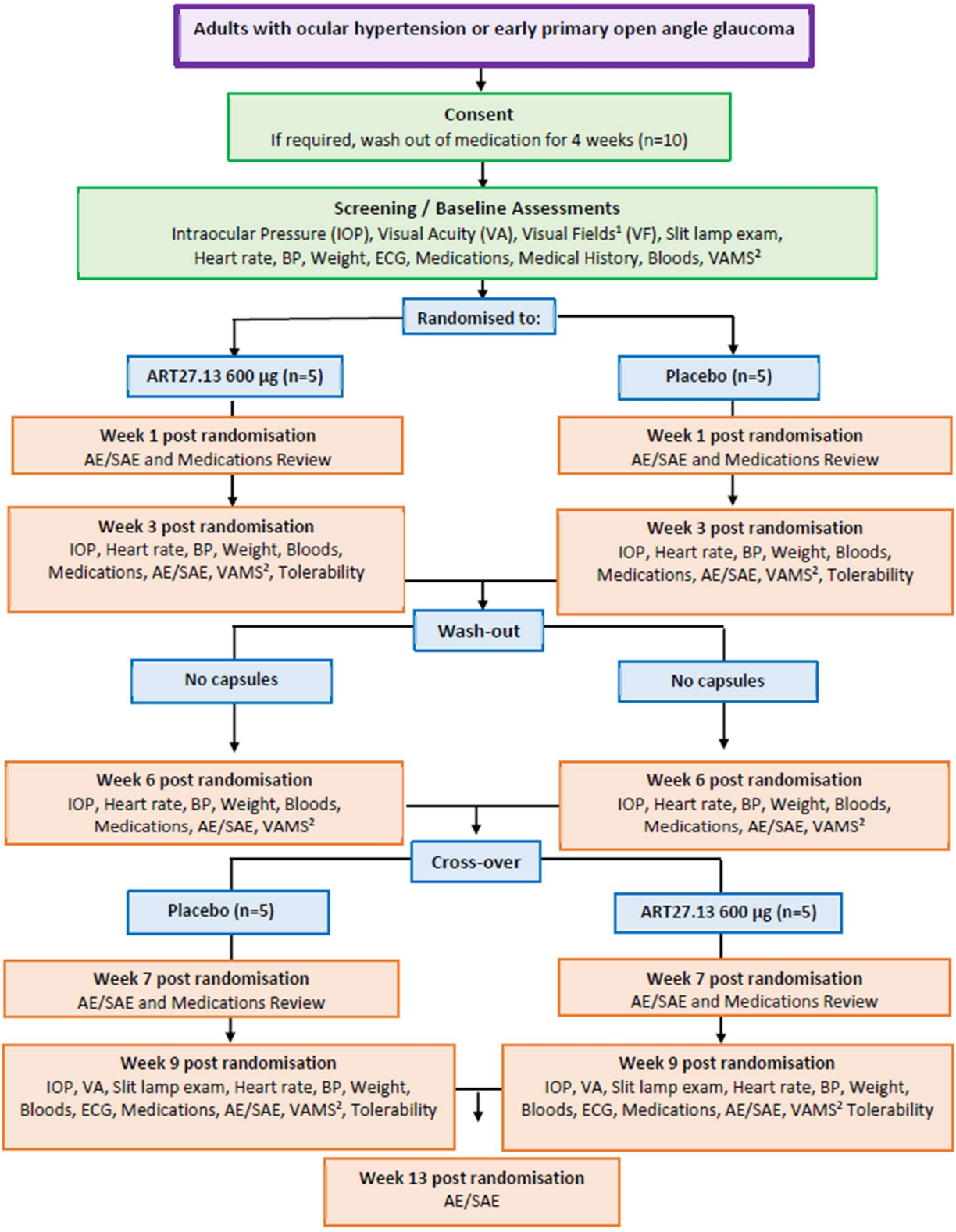
6 STUDY DESIGN

6.1 Study Design

A pilot, randomised, double-masked, placebo-controlled, single site, cross-over trial.

6.2 Study Schematic Diagram

The flow diagram depicting an overview of the trial is presented in Figure 1.



[1] Visual fields only required if they haven't been carried out on the participant in the last 6 months
[2] Visual Analogue Mood Scale (VAMS)

Figure 1. Flow diagram for the DREAM Study

6.3 Study Timelines

There will be a 12-month set up period to allow for contracting, regulatory applications, site set up, and training. Patient recruitment has been estimated at 4 patients per month over a period of 3 months. As some patients may require a 4-week wash out period, there is a 9-week treatment period and 4-week follow up period, it is anticipated that patient recruitment, treatment and follow up will be completed within a 6-month period. Analysis of the primary and secondary outcomes and dissemination of the study results will take place following trial completion.

6.4 End of Study

For the purposes of submitting the end of trial notification, the end of trial will be considered to be when the database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency
- Mandated by the Sponsor e.g. following recommendations from the DMEC
- Funding ceases

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the clinical trial authorisation will be notified when the trial has been concluded or stopped early.

7 TRIAL SETTING AND PARTICIPANT ELIGIBILITY CRITERIA

7.1 Trial Setting

Patients will be screened and recruited from the Glaucoma Service of the Belfast Health and Social Care Trust (BHSCT). The study visits and assessments will be carried out at the Northern Ireland Clinical Research Facility (NICRF).

7.2 Trial Population

All participants who meet the study inclusion criteria will be entered into a screening log. If the participant is not enrolled, the reason will be recorded.

7.3 Eligibility Criteria

Eligibility to participate in the trial will be confirmed by a physician who is named on the Delegation Log. Participants will be eligible to participate in the study in accordance with the following criteria. The ocular criteria must be met in one or both eyes.

7.3.1 Inclusion Criteria

1. Age ≥ 40 years for males, ≥ 55 years for females
2. Ocular hypertension or early primary open angle glaucoma (visual field loss less severe than -6 dB in a standard 24-2 Humphrey visual field test)
3. IOP between 20 and 35 mmHg inclusive*

*The patient's IOP at randomisation must fall between 20 and 35 mmHg inclusive, in either an untreated or washed-out state.

7.3.2 Exclusion Criteria

1. Any other clinically significant ocular disease in either eye
2. Current liver disease or laboratory results with elevated levels of liver transaminases (AST or ALT >3 x upper limit of normal (ULN) at screening visit)
3. Renal failure (eGFR <30 mL/min/1.73m² at screening visit)
4. Heart disease (e.g. myocardial infarction or arrhythmia)
5. Diagnosed with cancer in the last 12 months (with exception of non-melanoma skin cancer)
6. Prior ocular laser treatment within previous 12 months of enrolment
7. Prior surgical treatment for glaucoma
8. Intraocular surgery within previous 12 months of enrolment
9. Use of cannabinoids for other purposes within 3 months of enrolment (with the exception of cannabidiol (CBD))
10. Woman of childbearing potential i.e has had a menstrual cycle in the last 12 months or has not been permanently sterilised.
11. Male participants with sexual partners who have not agreed to use a condom during treatment and for 1 month after the last dose is administered.
12. Current use of systemic beta-blockers
13. Within 4 weeks prior to enrolment been on or expected to be on medications that are known to be strong cytochrome P450 CYP3A4 inhibitors or inducers
14. Within 4 weeks prior to enrolment been on or expected to be on medications that are known to be P-glycoprotein (PgP) Inhibitors or Substrates
15. Any clinical condition that, in the investigator's opinion, would make the participant unsuitable for the trial
16. Non-English speaking patients or those who do not adequately understand verbal or written information
17. Any known allergy to the active ingredient or excipients
18. History of any recreational or illicit drug use, alcohol misuse, or other drug misuse within the last 24 months.
19. Any history of depression in the last five years or current use of anti-depressant medication.
20. Not agreed to abstain from driving or operating heavy machinery for the first 4 weeks of each treatment cycle or longer if AEs warrant.
21. Total serum bilirubin > 1.5 x upper limit of normal
22. Any history of suicidal behaviour or serious suicidal ideation, defined as Category 4 or greater on the Columbia Suicide Severity Rating Scale (C-SSRS) at screening.
23. Declined consent

7.4 Co-enrolment Guidelines

Participants in the DREAM study may be eligible for co-enrolment in other studies, and this will be decided on a case-by-case basis by the CI. Participants enrolled in other investigational drug studies are not candidates for this study. Participants enrolled in other observational studies are potential candidates for this study.

8 SCREENING AND CONSENT

8.1 Screening Procedure

Patients that may be potentially eligible participants for the DREAM trial will be identified by a member of the direct care team through the Glaucoma Service of the BHSCT. Patients who have been initially diagnosed at the BHSCT and devolved to the community for standard follow-up care will be eligible for screening. A member of the direct care team will introduce the study to potential participants and provide the Patient Information Summary Sheet and/or Patient Information Sheet either face to face or by post. An invitation letter will be sent where information is being received by post.

If the patient is interested, they will be introduced to a member of the research team and presented with the participant information sheet, consent form and provided with a verbal explanation of the study. Following review of this information by the patient, and if they are still interested in participating in the study, a visit to the research clinic will be scheduled where consent and screening will take place. Patients who consent and are eligible will be enrolled on the study and recorded in the study database.

If patients are currently using IOP-lowering medication, a 4 week wash-out period of glaucoma medications will commence, after which a baseline visit will be scheduled. Following washout of glaucoma medications, the eligibility of patients will be reconfirmed at the baseline visit.

If the patient's IOP has increased to more than 35 mmHg at any point in the study, or has increased more than 10 mmHg from the baseline reading, ocular hypotensive medication will be reintroduced, see section 10.11 for further details. They will not proceed with randomisation and this will be documented on the electronic case report form (eCRF). They will be followed for safety until any adverse events (AEs) are resolved or stabilised. Any adverse events (AEs) or serious adverse events (SAEs) that have occurred should be reported as outlined in section 15 of the protocol.

If the patient is reconfirmed as eligible they will be randomised as outlined in section 9.2 of the protocol.

For patients not requiring wash out (e.g., newly referred to the glaucoma clinic), the baseline assessments will be carried out as part of the first screening visit and a separate baseline visit will not be necessary. If the patient is confirmed as eligible they will be randomised as outlined in section 9.2 of the protocol.

The PI or designee will be required to submit screening data to the CTU each month. Monthly screening data will be used to monitor participants screened, enrolled and randomised. A minimal dataset will be recorded for all participants screened and who meet the inclusion criteria, which will include age, ethnicity and sex.

8.2 Informed Consent Procedure

The PI (or designee) is responsible for ensuring that informed consent for trial participation is given for each participant. An appropriately trained member of the research team may take consent. The person taking informed consent must be Good Clinical Practice (GCP) trained, suitably qualified and experienced, and have been delegated this duty on the delegation log.

Appropriate signatures and dates must be obtained on the informed consent documentation prior to commencing the wash out period (if required), and/or randomisation. If no consent is given the participant cannot be enrolled into the trial.

8.3 Withdrawal of Consent

The patient may withdraw consent from the study at any time without detriment. If consent is withdrawn, this will be documented in the participant's medical notes and in the eCRF. If the patient declines on-going participation, safety data acquired up to the point of withdrawal will be used in the study analysis.

8.4 General Practitioner (GP) Contact

A letter will be sent to the participants GP to advise them of their participation in the DREAM study. The participants GP should also be contacted and informed of any incidental findings that are of clinical significance, for example an abnormal ECG result.

9 RANDOMISATION

9.1 Allocation Concealment Mechanism

The randomisation sequence will be generated by the trial statistician from the Northern Ireland Clinical Trials Unit (NICTU). The randomisation sequence will be saved in a restricted section of the TMF, which can only be accessed by the trial statistician and not those who will enrol participants.

9.2 Recruitment and Randomisation Procedure

After informed consent has been obtained and eligibility has been confirmed, a participant will be considered enrolled in the DREAM trial. Eligible participants will subsequently be randomised. Baseline assessments must be completed prior to study enrolment.

Note: If a 4 week wash out period is required, eligibility should be reconfirmed and baseline assessments completed, prior to randomisation.

Recruitment will be completed by an appropriately trained and delegated member of the site research team. The site should submit the Eligibility Checklist to the NICTU at DREAM@nictu.hscni.net. The NICTU will assign a unique Participant Number and confirm the eligibility of the participant by email to the site and local pharmacy. Pharmacy will hold the randomisation sequence, which will include the treatment allocation, and will release the allocated treatment to the participant.

The Participant Number assigned at the time of recruitment will be used throughout the trial for the purposes of patient identification. An entry will be recorded in the participants' medical notes noting recruitment into the study.

9.3 Unmasking Procedure

As a double-masked placebo controlled trial, patients, clinicians and the PI will be masked to treatment allocation. Participants will be given a Participant Study Card when they are recruited on to the trial. This will include 24-hour contact details of their treating clinician in the event that the patient needs to contact their clinician. Emergency unmasking may be requested on safety grounds, or if the treatment decision for a patient could be influenced by the knowledge of what the patient is taking as

part of the trial. If there is justification to unmask a patient, emergency unmasking will be performed by the Belfast Trust Pharmacy/On Call Pharmacist.

In the event unmasking occurs and the patient discontinues study drug, the patient will be followed for safety until any adverse events (AEs) are resolved or stabilised. Any adverse events (AEs) or serious adverse events (SAEs) that have occurred should be reported as outlined in section 15 of the protocol. Where unmasking has occurred this should be fully documented by the site and NICTU informed.

10 STUDY INVESTIGATIONAL MEDICINAL PRODUCTS

10.1 Risk Benefit Considerations of the Intervention

The acute toxicity of the medication is very low. Unwanted side effects occur not uncommonly but are generally well tolerated by patients. The most common adverse events observed in clinical studies are postural dizziness, nausea, hypotension and headache, all mild to moderate in severity. Other side effects include dry mouth, fatigue, back pain, malaise and an increase in alanine transaminase (ALT). ART27.13 may also stimulate appetite and lead to weight gain.

As known AEs of ART27.13 include dizziness and somnolence, caution should be taken around driving or operating heavy machinery. Participants will be not be able to drive for the first 4 weeks of each treatment cycle, this includes weeks 1 to 4 then again at weeks 7 to 10.

10.2 Study Drug Regimen

At the baseline visit, patients will be randomised to ART27.13 or matching placebo. Patients will be dosed orally with ART27.13 (600 µg once daily in the morning) or matching placebo for 3 weeks.

After 3 weeks of treatment the patients will complete a 3 week wash out period.

After completion of the 3 week wash out period the patients will cross over and receive the alternative treatment for another 3 weeks. (See Figure 1, section 6.2).

10.3 Study Drug Supply

Study drug is provided by Artelo Biosciences. Capsules will be manufactured, packaged and labelled by SGS United Kingdom Ltd. The investigational medicinal product (IMP) ART27.13 is formulated as a solid oral capsule. ART27.13 is manufactured as a 200 µg dose; therefore patients will be requested to take 3 capsules each day.

ART27.13 and matching placebo will be packed into high density polyethylene (HDPE) bottles with a polypropylene, child-resistant, twist-off cap, and will be labelled in compliance with the applicable regulatory requirements. Each bottle will contain 32 capsules.

Study drug packs will be dispatched by SGS United Kingdom Ltd to the pharmacist named on the study delegation log at the participating site under the instruction of the Trial Manager.

10.4 Study Drug Accountability

The BHSCT Pharmacy will maintain accurate records of all Investigational Medicinal Product (IMP) received (including for example date of receipt, batch numbers, expiry date), dispensed and returned on the Drug Accountability Log. Records must be available to the study monitors on request. Unallocated, unused and used study drug will be destroyed at site with permission from the CTU and

in accordance with site pharmacy procedure for destruction of IMP and hospital waste management policies. A record of the destruction will be maintained.

10.5 Study Drug Storage

BHSCT Pharmacy must ensure all study drugs are stored in a secure area and held separately from normal hospital stock and under the manufacturer's recommended storage conditions. ART27.13 requires storage at controlled ambient temperatures 15°C – 25°C and protected from light.

10.6 Study Drug Dispensing

When a patient is to be recruited, the PI or designee will contact the NICTU to recruit the patient and obtain the unique Participant Number assigned to the patient Visit 1 (Baseline). The PI or designee will complete a trial prescription form detailing the unique Participant Number and present this to pharmacy.

The NICTU will send a confirmation email to the site pharmacy confirming the recruitment of the participant and the unique Participant Number assigned. Pharmacy will dispense study drug packs for the Participant Number assigned in accordance with the randomisation schedule at Visit 1 (Baseline).

Study medication should also be dispensed at Visit 3 (Week 6). The site research team should liaise with Pharmacy who will dispense study drug packs for the Participant Number assigned in accordance with the randomisation schedule at Visit 3.

10.7 Study Drug Administration

Patients will be dosed orally with ART27.13 (600 µg once daily) or matching placebo for 21 days (+5 days or -2 days to allow for clinical visit scheduling). Three 200 µg capsules (white) or matching placebo, will need to be taken by the patient per day, in order to achieve the correct daily dose of 600 µg. Patients will commence study medication on the day of the baseline visit.

Study medication should be administered in the morning. If the study medication is not taken in the morning, it can be administered up to 12 hours later. Two doses should not be taken on the same day.

A telephone call should be completed by the research team 1 week after the patient has commenced study drug to assess if the patient is experiencing any side effects. The investigator should arrange an unscheduled visit if there are any safety concerns.

After 3 weeks of treatment, the patient will complete a 3 week wash out period (week 4 to week 6).

After completion of the 3-week wash out period, the patient will cross over and receive the alternative treatment for another 3 weeks (week 7 to week 9).

A telephone call should be completed by the research team at week 7, which is 1 week after the patient has recommenced study medication to assess if the patient is experiencing any side effects. The investigator should arrange an unscheduled visit if there are any safety concerns.

10.8 Study Drug Overdose

In case of a known or suspected overdose, symptomatic treatment should be given, and vital functions should be monitored. Study drug should be terminated as outlined in section 10.10.

10.9 Study Drug Adherence

Patients will be asked to store the medication according to the manufacturer's instructions. Patients should be asked to bring all unused medication and empty bottles to each visit. Research staff will perform a count and return any unused medication and empty bottles to the site pharmacy. Patients who have taken 80% or more of the expected number of capsules will be considered compliant.

10.10 Study Drug Termination Criteria

Study drug will be discontinued if any of the following conditions are met:

(1) Patient requests termination of study drug.
(2) Patient withdraws consent for the study.
(3) Decision by the PI that the study drug should be discontinued on safety grounds.
(4) Any relative increase in IOP of 10 mmHg from baseline.
(5) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level > 3 or total serum bilirubin > 1.5 x upper limit of normal (ULN).
(6) Requirement of a prohibited therapy as additional treatment
(7) A score of Category 4 or greater on the Columbia Suicide Severity Rating Scale (C-SSRS) at any visit prior to commencing with IMP

If the participant no longer wishes to receive the study drug or withdraws consent, the study drug will be terminated, and the investigator will arrange a follow up call at 4 weeks to assess safety.

If study drug is terminated due to an adverse event (AE), the investigator will arrange follow-up call/visit until the adverse event has resolved or stabilised. Any acquired safety data will be used in the analysis. The reason for study drug termination should be recorded on the eCRF and any unused medication returned to pharmacy.

10.11 Rescue Treatment and Concomitant Care

Patients will remain without additional licensed glaucoma treatment during the trial. However, if IOP increases above 35 mmHg or increases 10 mmHg from baseline reading, study drug should be stopped and glaucoma treatment should be commenced by the study team. Patients will return to standard of care treatment and usual clinical management. Study drug will not be available to patients at the end of the study.

Patients will be asked about all medications taken within 14 days prior to randomisation and commencing study drug, and at each subsequent visit. All medications taken by the patient should be documented in the eCRF. A list of prohibited medications is included in Appendix 1.

10.12 End of Study Drug

Following the completion of study drug at week 9 or if study drug is terminated earlier than week 9, patients will return to standard of care treatment and usual clinical management. Study drug will not be available to patients at the end of the study.

11 SCHEDULE of ASSESSMENTS

11.1 Participant Assessments

The frequency of assessments and follow up are detailed in the schedule of assessments (Table 2). The schedule defines the timing of assessment visits (with visit windows) necessary for data collection. Participants should be followed until the final follow-up assessment at week 13, unless study drug is terminated early. If study drug is terminated early, participants should be followed 4 weeks post study drug termination for safety assessments.

Table 2: Schedule of Assessments

Day/Timepoint	Screening	Baseline	Day 7 +5/-2 days	Day 21 +5/-2 days	Day 42 +5/-2 days	Day 49 +5/-2 days	Day 63 +5/-2 days	Day 91 +5/-2 days
At Hospital/Remote	Hospital	Hospital	Remote	Hospital	Hospital	Remote	Hospital	Remote
Consent	x							
Eligibility	x	x						
Demographics	x							
Physical Exam[1]	x						x	
Vital Signs: Heart Rate[2], Blood Pressure[2], Weight	x	x		x	x		x	
Medical History	x							
ECG[3]	x						x	
Medications[4]	x	x	x	x	x	x	x	
IOP[2,5]	x	x		x	x		x	
Habitual Visual Acuity	x						x	
Visual Fields[6]	x							
Slit Lamp Exam	x						x	
Routine Safety Bloods[7] Full Blood Count	x			x	x		x	
Visual Analog Mood Scale (VAMS) Questionnaire[8]		x		x	x		x	
Randomisation		x						
IMP administration / Adherence		x	x	x	x	x	x	
Tolerability - Drug Abuse Potential Questionnaire[9]				x			x	
C-SSRS Questionnaire[10]	x			x			x	x
Adverse Events/ Serious Adverse Events	x	x	x	x	x	x	x	x

[1]Physical exam will cover head and neck including lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, neurological systems and others as applicable. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion. Any abnormality identified at baseline should be recorded on the Medical History eCRF. Changes from baseline abnormalities should be recorded in the participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs.

[2] Determination of IOP, heart rate and blood pressure should be made at the same time of the day (+/- 2 hours) due to diurnal variation.

[3]An electrocardiogram (ECG) will be performed at screening and week 9, additional ECGs may be performed if clinically needed. If an ECG has been performed within the last 6 months and has shown as normal, this can be used as the screening ECG.

[4]Medications taken within 14 days prior to the first dose of study medication should be recorded. Medications started or stopped during the treatment period should be recorded at every visit up to week 9. See Appendix 1 for a list of prohibited medications.

[5]To determine the IOP the average of two GAT readings of IOP will be used. A third reading should be taken if the difference between the first two readings is greater than 3 mmHg.

[6]At the screening visit a Humphrey 24-24 threshold visual field exam should be completed. However, if a visual field exam has been completed within the previous 6 months, a visual field exam does not need to be repeated as long as results are available.

[7]Routine Safety Blood Samples (up to 10 mls) should be obtained at each clinic visit and include: Liver Function Test (LFT) profile (AST, ALT, ALP, GGT, Albumin and Total serum bilirubin) and a full Urea and Electrolyte (U&E) profile (Sodium, Potassium, Chloride, CO_2, Urea and Creatinine)

[8]In order to determine the tolerability of the drug, participants will be asked to rate the extent to which they feel each of the following five experiences signified by the adjectives 'stimulated', 'high', anxious', 'sedated' and 'down' using a visual analogue mood scale (VAMS), and marking on a scale of 0-10, 0 being not at all and 10 being extremely (57). This will be done at baseline then again at weeks 3, 6 and 9.

[9]Participants will also be asked to complete a Drug Abuse Questionnaire at week 3 and week 9 (58). The human abuse potential (HAP) of ART27.13 will be determined from an assessment of AEs that might suggest HAP such as euphoria, hallucination, and dissociative state.

[10]Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire will be used at screening and again after treatment (days 21 and 63) and as part of the final check on day 91. This questionnaire assesses the severity and immediacy of suicide risk. The PI is responsible for ensuring if a patient scores as category 4 or above they are directed to the appropriate support services

11.2 Participant Follow-Up at Week 1, Week 7 and Week 13

Follow up assessments will be performed by an appropriately trained member of the clinical research team via telephone at week 1, week 7 and week 13 to assess safety.

12 DATA COLLECTION and MANAGEMENT

12.1 Data Collection

To ensure accurate, complete, and reliable data are collected, the CTU will provide training to site staff. All data for an individual participant will be collected and recorded in source documents and transferred onto a bespoke, web-based, electronic CRF for the study. A data dictionary, record of automatic and manual data queries, and a full audit trail, will ensure data captured are consistent, reliable, and fully compliant with GCP and any other relevant regulatory requirements. For routinely collected clinical data, the NHS record will be the source document. Participant identification on the CRF will be through their unique participant study number, allocated at the time of randomisation. Data will be collected and recorded on the electronic CRF by the PI or designee as per the CRF submission guidelines.

12.2 Data Quality

The CTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Source data verification (SDV) will be completed by the CTU and will check the accuracy of entries on the electronic CRF against the source documents and adherence to the protocol. The extent of SDV to be completed is detailed in the Monitoring Plan.

Quality control is implemented by the CTU in the form of Standard Operating Procedures (SOPs), which encompass aspects of the clinical data management process, and ensure standardisation and adherence to GCP guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

A DMEC will be convened for the study to carry out reviews of the study data at staged intervals during the study.

12.3 Data Management

Following the entry of participant data into the study database, the data will be processed as per the CTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated electronically for site staff to clarify data or provide missing information, with the expectations that these queries will be completed within 14 days of receipt. All queries will be responded and amended within the study database.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

In the Early Manifest Glaucoma Trial (56), the standard deviation of untreated IOP over time was 2.02 mmHg and 1.78 mmHg in the untreated and treated arms, respectively. We have used a SD of 2 mmHg for our sample size estimation. With a sample size in each sequence group of 5, (a total sample size of 10) a 2 x 2 crossover design will have 90% power to detect a difference in mean IOP of 2.4 mmHg, assuming that the Crossover ANOVA sqrt (MSE) is 1.414 (the Standard deviation of differences, σ, is 2) using a two group t-test (Crossover ANOVA) with a 0.05 two-sided significance level. A difference above 2 mmHg in IOP is considered to be clinically important by European glaucoma experts (European Glaucoma Society consensus survey) [53].

13.2 Data Analysis

13.2.1 Analysis Population

All participants that complete both periods (IMP and placebo) will be included in the analysis population therefore our primary analysis will be ‘per protocol’. If a participant stops the study drug, or participation in the trial for any reason, we will recruit another participant until we have 10 completing the trial. At baseline visit, where both eyes meet the inclusion criteria, we will define a study eye for the main analysis, i.e., the eye with highest IOP. In case of both eyes having similar IOP the study eye will be the one with more advanced disease. Trial results will be reported in accordance with Consolidated Standards of Reporting Trials guidance (CONSORT) [54].

13.2.2 Statistical Methods

We will describe baseline characteristics, follow-up measurements and safety data, using suitable measures of central tendencies; means and medians with the associated standard deviations/95% confidence intervals and interquartile ranges for continuous data; and frequencies and proportions for categorical data (including binary data).

For the primary outcome the treatment effect will be analysed using a linear mixed effect model with subject as a random effect estimating mean difference and 95% CI.

Analyses will be two-sided and tested at an a priori significance level of p=0.05. A statistical analysis plan will be approved before completing data collection.

13.3 Missing Data

If a participant drops out during the trial, we will recruit another participant until we have 10 completing the trial. Therefore, we do not envisage missing data to be a problem in this trial.

14 PHARMACOVIGILANCE

14.1 Definition of Adverse Events

Table 3: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Suspected unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation* • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect 'Important medical events' may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the

	event; it does not refer to an event which hypothetically might have caused death if it were more severe.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

14.2 Adverse Event Reporting

The AE reporting period for the trial begins upon consent and ends at week 13 (the last follow up assessment). However, if study drug is terminated early, participants should be followed 4 weeks post study drug termination for safety assessments.

The PI or designee should record all directly observed AEs and all AEs spontaneously reported by participants. In addition, participants will be asked about AEs as part of the follow up assessments to be completed.

14.3 Assessment of Causality

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the intervention (Table 4).

Table 4. Categories of causality for adverse events

Category	Definition
Definitely*	Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.
Probably*	Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
Possibly*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
Unlikely	Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
Not Related	Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

* Where an event is assessed as possibly, probably, or definitely related, the event is an adverse reaction (AR).

14.4 Assessment of Severity

The PI or designee should make an assessment of severity according to the following categories (Table 5).

Table 5. Categories of severity for adverse events

Category	Definition
Mild (Grade 1)	A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with everyday activities.
Moderate (Grade 2)	A reaction that is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3)	A reaction that prevents normal everyday activities.

Life Threatening (Grade 4)	A reaction that has life threatening consequences; urgent intervention indicated.
Death (Grade 5)	A reaction that results in death.

14.5 Assessment of Seriousness

The PI or designee should make an assessment of seriousness on the basis that it:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
  Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

14.6 Assessment of Expectedness

The reference safety information is the Investigators Brochure (IB) section 6.2 for oral cannabinoid ART27.13 as approved by the MHRA.

The PI or designee is required to make an assessment of expectedness for ARs if the event is possibly, probably or definitely related to the study drug. Given that there were no SAEs reported in the previous studies of ART27.13, all SAEs with a reasonable possibility of being associated with the use of ART27.13 will be considered unexpected for the purposes of expedited (Suspected, Unexpected, Serious Adverse Reaction; SUSAR) reporting.

14.7 Recording and Reporting of Adverse Events and Serious Adverse Events

AEs and SAEs should be recorded in the medical notes of the participant in accordance with GCP.

AEs are to be recorded on the Adverse Event Form within the CRF and submitted to the CTU as per the CRF submission schedule.

A SAE is defined as an AE that fulfils one or more of the criteria for seriousness outlined in section 15.5. SAEs will be evaluated by the PI or designated investigator for causality (i.e. their relationship to the study drug) and expectedness (if the event was deemed to be related).

SAEs are to be recorded on the Serious Adverse Event Form. SAEs should be reported to the CTU within 24 hours of the investigator becoming aware of the event, by email to clinicaltrials@nictu.hscni.net. All SAEs should also be reported on the AE Form within the CRF.

The site should not wait until all information about the event is available before notifying the CTU of the SAE. The CTU will acknowledge receipt of the SAE Form by email to the site. Information not available at the time of the initial report must be sought and submitted to the CTU as it becomes available.

14.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be related to the intervention and are unexpected.

The CTU is responsible for reporting SUSARs to the Sponsor, MHRA and REC (if applicable) within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the CTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported within 15 days after the knowledge of such an event.

14.9 Recording and Reporting Urgent Safety Measures

The Sponsor and investigator may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. The investigator may implement urgent safety measures without prior approval from the REC or MHRA.

When a PI becomes aware of information that necessitates an urgent safety measure, they should phone the MHRA Clinical Trials helpline (020 3080 6456) and discuss the issue with a safety scientist or medical assessor within 24hrs.

The PI or designee should report the urgent safety measure to the CTU immediately, by email to clinicaltrials@nictu.hscni.net.

The CTU will report the urgent safety measure to the CI and to the Sponsor immediately, using the dedicated email address: clinical.trials@belfasttrust.hscni.net. The CI will notify the MHRA and the REC (if applicable) providing full details of the information they have received and the decision-making process leading to the implementation of the urgent safety measure within the timelines as required by the UK Clinical Trial Regulations.

The PI or designee should respond to queries from the Sponsor or CI immediately to ensure the adherence to reporting requirements.

14.10 Pregnancy Reporting

Pregnancy is not considered an AE or SAE, however an abnormal outcome would be. Woman of childbearing potential are excluded from the DREAM trial, therefore the PI or designee must collect pregnancy information for females who become pregnant while their partners are participating in the trial. Consent should be obtained to follow up the pregnancy from the female partners of male participants.

The pregnancy reporting period for the trial is from the commencement of the study drug until 4 weeks post study drug termination. The PI or designee should complete and submit the Pregnancy Reporting Form to the CTU by email (clinicaltrials@nictu.hscni.net) within 14 days of being made aware of the pregnancy. The CTU will acknowledge receipt of the Pregnancy Reporting Form by email to the site.

Any pregnancy that occurs in a participant's partner during the trial should be followed to outcome. Follow up/outcome information should be provided to the CTU as soon as it becomes available.

An unwillingness to undertake adequate precautions to prevent pregnancy for the duration of the trial will result in exclusion from the study.

15 DATA MONITORING

15.1 Data Access

The PI must facilitate trial related monitoring, audits, ethics committee review and regulatory inspections, by providing access to source data and trial related documentation. Each participant's confidentiality will be maintained, and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

15.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. The frequency and type of monitoring (on site and/or remote) will be detailed in the monitoring plan and agreed by the Sponsor.

Before the trial starts at the participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of participant recruitment and follow up.

The PI or designee should ensure that the monitor can access all trial related documents (including source documents) that are required to facilitate the monitoring process. The extent of source data verification (SDV) will be documented in the monitoring plan.

16 REGULATIONS, ETHICS AND GOVERNANCE

16.1 Regulatory and Ethical Approvals

The trial will comply with the principles of GCP, the requirements and standards set out in the UK policy framework for health and social care research and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee (REC) and clinical trial authorisation (CTA) will be obtained from the MHRA before the start of the trial.

The trial protocol is prepared in compliance with the SPIRIT 2013 statement [55] and the trial will be registered at https://www.isrctn.com/ before randomisation of the first participant.

16.2 Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the REC and the MHRA. A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented. A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that any potential serious breaches are reported directly to the CTU within one working day using the dedicated email address (clinicaltrials@nictu.hscni.net).

The CTU will notify the CI and Sponsor immediately to ensure adherence to reporting requirements to REC and MHRA where a serious breach has occurred. Protocol compliance will be monitored by the CTU to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs and participant consent forms) is being completed appropriately.

16.3 Protocol Amendments

All protocol amendments will be undertaken in accordance with the regulatory requirements. Substantial changes to the protocol will require REC and MHRA approval prior to implementation, except when modification is needed to eliminate an immediate hazard to participants.

16.4 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

16.5 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to participants through the Clinical Negligence Fund in Northern Ireland. Queen's University Belfast will provide indemnity for negligent and non-negligent harm caused to participants by the design of the research protocol by Queen's University Belfast staff.

16.6 Participant Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the participants by their unique participant study number and initials only. Participant confidentiality will be maintained at every stage, and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

16.7 Record Retention

The site PI will be provided with an Investigator Site File (ISF) by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for the archiving of essential documents at their site for 25 years in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor on request. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

The TMF will be held by the CTU within the BHSCT and the essential documents that make up the TMF will be listed in a SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and as required by the BHSCT as Sponsor.

16.8 Competing Interests

The research costs are funded by Glaucoma UK and the Public Health Agency (PHA), Health and Social Care (HSC) Research & Development Division, Northern Ireland. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC will be asked to

confirm that they have no conflict of interest. In the event that a member of the DMEC reports a conflict of interest, advice will be sought from the Sponsor.

17 DISSEMINATION/PUBLICATIONS

17.1 Publication Policy

It is anticipated that the study findings will be published in national and international peer reviewed journals and these articles will be led by the CI. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health-care professionals. In addition, study findings may be presented at both national and international meetings and to appropriate patient groups. Participants involved in the trial will be provided with a lay summary of the principal study findings.

17.2 Contributors and Authorship Policy

Augusto Azuara-Blanco (AAB), Lucia Dalton (LD) and Emma McConnell (EMcC) conceived the study, and initiated the study design, and are grant holders. Mike Clarke (MC), Director of NICTU and Cliona McDowell (CM), Head of Statistics NICTU, contributed statistical expertise in clinical trial design. All of the above, including Margaret McFarland (MM), BHSCT Clinical Trial Pharmacist, Lynn Murphy (LM), NICTU Manager and Megan Campbell (MC), Trial Manager, contributed to the protocol development. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

In brief, an author will be considered to be someone who has made a substantive intellectual contribution to the study and the relevant report. All investigators, Trial Statistician and relevant members of the TMG can potentially be co-authors. Collaborators including Artelo will be acknowledged.

17.3 Data Access/Sharing

Following publication of the primary and secondary outcomes there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI via the CTU, who will discuss the request with the Sponsor. Data sharing will be undertaken in accordance with the required regulatory requirements. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission.

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19 APPENDICES

19.1 Appendix 1: PROHIBITED MEDICATIONS

Strong inhibitors or inducers of CYP3A4 are not permitted at any time during the study. Examples of these medications are listed in the table below. This list is not exhaustive and the same restriction applies to other agents known to affect CYP3A4 activity. Appropriate medical judgement is required, contact the study team with any queries.

CYP3A4 Inhibitor (strong)	**CYP3A4 Inducer (strong)**
Ceritinib	Carbamazepine
Clarithromycin	Enzalutamide
Cobicistat	Mitotane
Danoprevir	Nevirapine
Dasabuvir	Phenobarbital
Elvitegravir	Phenytoin
Grapefruit juice	Rifabutin
Idelalisib	Rifampin
Lopinavir	St. John's wort
Itraconazole	Troglitazone
Ketoconazole	ivosidenib
Nefadozone	Rifapentine
Nelfinavir	Apalutamide
Ombitasvir	Lumacaftor
Paritaprevir	-
Ritonavir	-
Saquinavir	-
Telithromycin	-
Tipranavir	-
Troleandomycin	-
Voriconazole	-
Indinavir	-
Telapravir	-
Mifepristone	-
Lonafarnib	-
Posaconazole	-
Conivaptan	-
Tucatinib	-
Nelfinavir	-
Ribociclib	-

Inhibitors or substrates of PgP are not permitted at any time during the study, a list of examples of these medications is provided in the table below. These lists are not exhaustive and the same restriction applies to other agents known to affect PgP activity. Appropriate medical judgement is required, contact the study team with any queries.

PgP Inhibitors	**PgP Substrates**
Cyclosporine	Digoxin
Elacridar (GF120918)	Fexofenadine
Ketoconazole	Loperamide
Quinidine	N-methylquinidine (NMQ)
Valspodar (PSC833)	Quinidine
Verapamil	Talinolol
Zosuquidar (LY335979)	Vinblastine

PgP = P-glycoprotein

In addition, induction of CYP3A4 and to a lesser extent 2B6, 2C8, 2C9 and 2C19 by ART27.13 has been shown in vitro. It cannot be excluded that ART27.13, upon co-administration, may reduce the exposure to substrates of these metabolic enzymes. Substrates of CYP3A4, 2B6, 2C8, 2C9 and 2C19 are prohibited during conduct of this pilot study.