The Altascientist
SCIENTIFIC JOURNAL
ISSUE NO. 27

THE COMPLEXITIES OF EARLY PHASE OPHTHALMIC DRUG DEVELOPMENT

How an end-to-end solution can facilitate a path to Phase II

Ophthalmic medications have a particular set of challenges that can impact their speedy and successful path to market. From prototype formulation through preclinical testing, early phase clinical and manufacturing and development, ophthalmic drug development presents with specific and unique complexities. It is best to entrust drug development to a partner with regulatory knowledge, technical expertise, and a thorough understanding of the market in this growing therapeutic area. From current reality to future trends, being at the forefront of ophthalmic drug development delivers tangible benefits to sponsors.

As the population continues to age, serious eye disorders have risen to the forefront as a public health concern. Given the complexity and potential devastation of many ocular diseases, vision-saving advancements in treatment and diagnosis are bringing new hope to patients, caregivers, and providers. Clinical studies in more durable therapies, new indications for existing treatments, gene therapy advances, and improvements in surgical intervention continue to progress towards slowing, stopping, and even reversing the progression of sight-threatening diseases.

While development of therapies for ophthalmologic disorders poses a range of unique challenges, from patient recruitment to trial design, continued progression of the science presents unprecedented opportunity to achieve great advances on behalf of patients. We are dedicated to finding solutions for people facing serious eye disorders with the ambition to save the sight of millions, and we continue to see the market evolve to include more convenient and effective options to protect people from blindness. These trends are encouraging to all those who are committed to improving the lives of those impacted by ocular disease as the need for new innovations continues to grow.

- Nancy Lurker
President, Chief Executive Officer and Director of Eyepoint Pharmaceuticals, Inc.

TABLE OF CONTENTS

Click to jump directly to the section:

INTRODUCTION

The global market for ophthalmic drugs was valued at USD 36.7 billion in 2020, according to Grandview Research.[1] The compound annual growth rate (CAGR) is expected to be 6.4% from 2021 to 2028. The acceleration in market growth is influenced by increasing awareness of eye-related diseases and advancements in related technology. The aging of the population, as well as the impact of COVID-19 ocular involvement are also contributing factors. Certain ocular diseases are quite rare, whereas others, such as cataracts, age-related macular degeneration (AMD), and glaucoma, are very common, especially in the aging population

Drug development in the ocular space has specific challenges. The eye is a multi-faceted organism, and has many barriers to drug delivery. Formulation and delivery options must be expertly planned and developed to overcome those barriers and ensure that the maximum bioavailability is achieved without negatively impacting vision or the physical structure of the eye. Planning of preclinical studies must consider the appropriate animal species for the route of administration and therapeutic area of the investigational drug. Some species are more appropriate for certain routes of administration, while others have relevant retinal mutations that can be leveraged in ocular development.

Clinical trials need to be carefully designed by knowledgeable specialists with significant ophthalmic experience. The delicate nature of the eye and the importance of subject safety are key considerations. Just as importantly, the bioanalysis of trial samples necessitates the use of bioanalytical techniques created especially for the often uncommon and frequently fragile matrices involved. Finally, understanding the regulatory environment and related guidances, as well as proactive and appropriate discussions with relevant agencies when warranted, are critical components of the pathway and can help ensure a seamless experience.

PROTOTYPE DEVELOPMENT, FORMULATION, AND MANUFACTURING (CDMO)

The ocular surface is a surprisingly diverse portion of the eye, consisting of multiple tissues and glands. Drug delivery to the internal ocular structures requires targeted strategies, due to the protective systems of the eye which limit the success of systemic treatments. Ocular treatments of any kind must be delivered for use in a sterile state.

Pharmaceutical treatment of ocular diseases has benefitted from permeability enhancers and advances in prodrug formulations, which allow for effective topical treatments. Current routes of administration that address they eye's drug delivery barriers include, from most to least popular:


Topical administration


Systemic administration


Intravitreal injections


Intraocular implants


Subretinal injections


Suprachoroidal injections

Each of these has unique characteristics that make it suitable for different applications.

Topical Administration

Eyedrops deliver medicine into the conjunctival fornix. However, only up to 20% of the administered drug is retained, with the remainder being drained into the nasolacrimal duct, which helps maintain the precorneal fluid volume. Therefore, the potency, bioavailability, and clearance of the drug at the target ocular tissue, as well as the material properties and size constraints of the eye, must all be considered for optimal formulation of drug delivery systems.

Prodrug formulations use pharmacologically inactive derivatives of drug molecules that are more lipophilic and thus have a better ability to penetrate the cornea. Following administration, the prodrug is metabolized to the active parent compound within the cornea. The majority of prodrugs are designed for topical use.

The addition of permeability enhancers to the drug formulation can increase corneal penetration into the anterior segments of the eye. Some of the available options include surfactants, bile acids, chelating agents, and preservatives

Cyclodextrins, cylindrical oligonucleotides with a hydrophilic outer surface and a lipophilic inner surface that form complexes with lipophilic drugs, are among the more popular permeability enhancers. They improve chemical stability and bioavailability while reducing local irritation, and have been used in particulate drug delivery systems.

Systemic Administration

Blood-ocular barriers, including tight junctional complexes in the ciliary body and retinal pigmented epithelium, nonfenestrated and iridial capillaries, and P-glycoprotein efflux pumps, are defense mechanisms to protect the eye from circulating antigens, inflammatory mediators, and pathogens. However, they also act as a considerable barrier to systemically administered drugs.

Injections

Ocular delivery from intravitreal, suprachoroidal, subconjunctival, and periocular sites to the posterior segment is a popular approach to support the development of new injectable and implantable prolonged-action dosage forms.

Suspensions and Nanosuspensions

Nanosuspensions are used to improve the bioavailability of insoluble or poorly soluble molecules, usually by dispersing them in an aqueous solvent. Particle size is directly indicative of drug residence time and activity on the precorneal surface–small particles replenish the drug absorbed by ocular tissue, while large particles are more easily retained and slow drug dissolution.

Suspensions require a dissolution or release of a drug prior to absorption. Release, ocular residence time, and bioavailability of a drug all vary based on the physicochemical properties of the suspension.

Nanosuspensions also improve the bioavailability of hydrophobic drugs by increasing solubility and residence time, although it must be noted that physical stability can be a challenge, and there is a potential for drug sedimentation. Ali et al[2] demonstrated a 1.8-fold improvement in the bioavailability of hydrocortisone when prepared as a nanosuspension as compared to the commercially available solution and Fisccella et al[3] demonstrated a therapeutic difference between generic and brand-name prednisolone due to such formulation differences.

Altasciences' CDMO has significant expertise in developing small molecule ocular drugs, including **nanomilling,** suspensions, and **pre-sterilized injectables.**

CDMO CASE STUDY

Altasciences has a **long-term relationship** with an ocular client, for whom we **regularly manufacture and perform analytical testing**. In order to accurately and consistently meet our client's needs, we:

Manage procurement logistics

- Efficiently coordinate and manage the procurement of a wide number of excipients, from different suppliers, ensuring that all quantities are received on a schedule that respects the client's timeline.
- Altasciences also has capabilities to procure specialized packaging components for any of our clients, although it is not required in this case.

Manufacture product

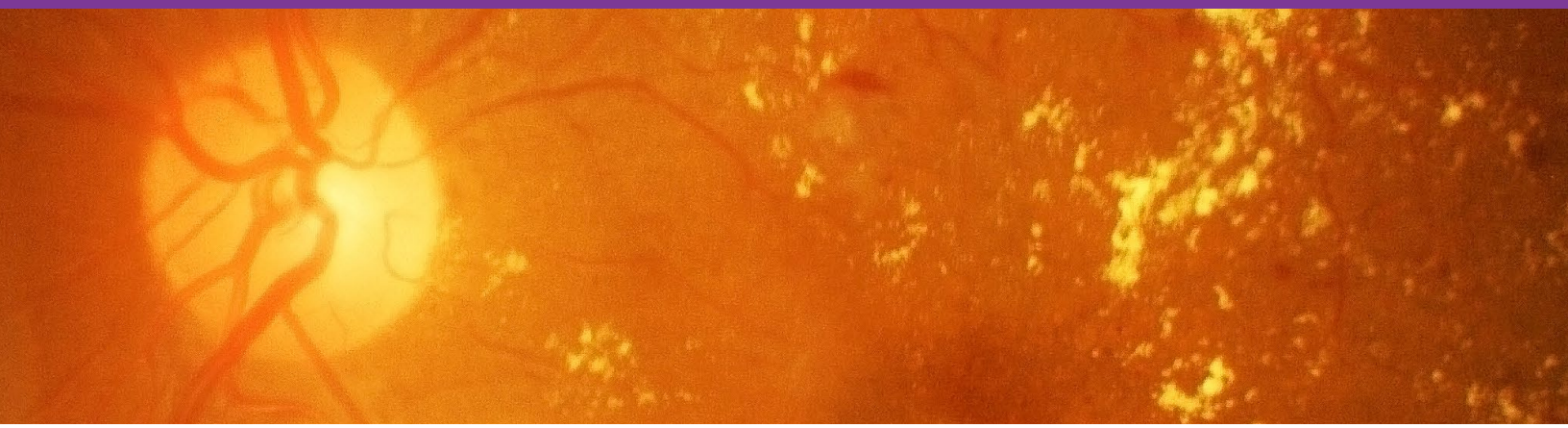
- Highly trained operators precisely mix the bulk product according to the client's formulation in Altasciences' Grade C compounding room, in a 7.4 kg batch size.
- Altasciences has the facilities and expertise to manufacture batch sizes from 1 kg to 100 kg, for ocular products (up to 2000 kg for other therapeutic areas), ready for bulk delivery, clinical trial, or commercial supply.
- Batch details for this client are confidential. However, using the latest, state-of-art equipment train, including Netzsch Deltavita mills, we can wet mill your active pharmaceutical ingredient (API) to reduce particles to meet nano size specifications.

Perform analytical testing

- A representative sample of the in-process material is tested for purity, particle size, and several other product quality tests in our onsite analytical lab, using spectrophotometric, chromatographic, and particle size analyzer technology. These tests allow Altasciences to precisely quantify the API and determine that the material has been milled to the correct specifications for downstream processing.
- In the unlikely event that testing determines the product does not meet specifications, an investigation into the root cause is immediately carried out, and a corrective and preventative action plan (CAPA) is put into place to prevent failure of future batches.

Sterilize (terminal sterilization)

- For this client, we send the bulk material for terminal sterilization. For other ocular development, we can bottle, apply band seals in a variety of colors or overprinting, and package prior to sending for terminal sterilization.



PRECLINICAL RESEARCH

Preclinical trial design for ocular drugs depends on the specifics of the drug in development, such as whether the drug product is a new chemical entity (NCE) or a reformulation of a previously approved drug.

Preparation for First-in-Human (FIH) Studies

When preparing for FIH studies of ocular drugs, two non-rodent species are preferred. Large species such as dogs and rabbits are suitable for drugs delivered in all routes: topical, subconjunctival, intracameral, subretinal, and intravitreal (IVT). Pigs are more suitable for subretinal and IVT injections and nonhuman primates (NHPs) are more suitable for subconjunctival, intracameral, subretinal, and IVT. Dogs and small species like rats and mice that carry retinal mutations similar to retinitis pigmentosa (RP) are best suited for subretinal injections for gene therapy. A single species may be acceptable in cases where there is sufficient rationale (i.e., lack of biologic homology in other species), or existing nonclinical and/or clinical data from other ocular administrations of the drug.

The conduct of ocular pharmacokinetic (PK) studies, to understand the absorption, distribution, metabolism, and excretion (ADME) in various ocular compartments, is common. Usually, a single species is sufficient, and target pharmacological relevance is not required.

Before considering pivotal repeat-dose ocular studies, an ocular tolerability study is recommended; usually, a single-dose study in a small number of rabbits. Typical dosing would be a 20 to 30 µl drop size in a single dose/concentration, with hourly observation and scoring (modification of the Draize scoring system), and concentration or dose frequency increases over several days, with complete ophthalmological evaluation by slit-lamp biomicroscopy and indirect ophthalmoscopy.

For pivotal toxicity studies, typical parameters for ocular evaluation include ophthalmic examinations, including biomicroscopy of the anterior segment, indirect ophthalmoscopy to examine the posterior segment, tonometry, ocular coherence tomography (OCT) or electroretinograms (ERG) if the drug reaches the retina, and histopathology. Systemic toxicokinetic (TK) analysis is typically performed, particularly when systemic tissues are being evaluated. Ocular TK is rarely performed because there is insufficient tissue for compartmentalization studies. Microscopic examination and ocular PK studies are thus acceptable. If necessary, other specialized procedures such as fluorescein angiography or vitreal PK may be performed.

Before FIH trials, a systemic evaluation of toxicity in at least one species using intravitreal or oral administration to maximize systemic exposure is generally expected, as are two *in vitro* genetic toxicity tests for mutation and clastogenicity. A full systemic evaluation in one or both species, as well as a separate study in one species, such as a rat, can be included in the ocular development program. When necessary, reproductive toxicity and safety pharmacology should be evaluated in accordance with ICH guidelines.

Species and Strain Selection Parameters

Nonrodents such as rabbits, dogs, and/or monkeys are usually the species of choice in ocular toxicity and pharmacokinetic studies. Due to the large size of their eye, rabbits are the most commonly used species for ocular toxicity testing. A nonpigmented rabbit strain, such as the New Zealand White (NZW), is usually acceptable when combined with a pigmented species (dog or primate). Minipigs are frequently used to study human ocular disease because the retina, pupil, and lens most closely resemble those of the human eye. Dogs are good models as different breeds carry different relevant mutations, and they have large eyes that allow for higher volume injections and treatment areas.

The anatomy and physiology of the monkey eye are most similar to that of the human eye, including the presence of a macula. NHPs are typically the first species chosen for biologics due to higher sequence homology and relevance to pharmacological responses in humans, as well as a lower risk of antigenic response to the test article. Dogs and small rodent species such as rats and mice, where strains with genetic retinal mutations are easily studied, are used for subretinal gene therapy injections.

Routes of Administration

Different formulations and routes of administration allow for optimal drug delivery and absorption in the target structure of the eye.

ROUTES OF ADMINISTRATION	FORMULATIONS
Topical	Liquid, suspension, ointment
Subconjunctival	Liquid, suspension, gel
Intracameral	Liquid
Intravenous	Liquid, suspension, gel, implants
Subretinal	Liquid, cell delivery

There are some important differences in ophthalmic preparations: a liquid formulation is quickly absorbed and releases drug rapidly but may require frequent administration. Ointment, gels, and implants are generally used for slow drug release, and require less frequent administration.

Specialized Ocular Assessments and Equipment

For subretinal injections, highly skilled scientists and specific equipment are needed. A specialized injection device with a 25-gauge needle penetrates the conjunctiva and the sclera. From there, when the tip of the needle approaches the retinal surface, a 39-gauge polyimide cannula is extended and brought into apposition with the retina for the subsequent subretinal injection of test article or adeno-associated virus (AAV). Using this procedure, closure of the conjunctiva is not required.

In vivo imaging after intravitreal and subretinal injections is performed via OCT and fundus photography. OCT is a non-invasive imaging technology that provides a cross-sectional view of the retina, the retinal-vitreal interface, and anterior ocular structures at near-cellular resolution. In fundus photography, a specialized low-power microscope is attached to a camera and examines structures such as the optic disc, retina, lens, and cornea. In preclinical studies, these technologies are used to help evaluate pharmacological or toxicological drug effects, and evaluate test article progression and possible toxicity to the retina/choroid.

PRECLINICAL CASE STUDY

Safety Assessment of Intravitreal Implants in Dutch Belted Rabbits

Study Overview

In support of their IND, Altasciences' client commissioned a chronic toxicology study to evaluate the ocular safety of a cylindrical intravitreal implant, which was loaded with an API intended for the treatment of age-related macular degeneration. Dutch belted (DB) rabbits were chosen based on (1) the historical use of this breed for ocular safety assessment, (2) the need for an animal model with pigmented eyes to evaluate the potential for ocular melanin binding, and (3) the availability of animals in sufficient quantity for an IND-enabling study.

As is often the case for nonclinical safety studies, the doses given to the rabbits needed to be several-fold higher than the human dose, which required that up to six implants be delivered to each eye. The large number of implants presented both technical and scientific challenges. Rabbits have a much smaller vitreous space (~1.5 mL total vitreous volume in rabbit versus ~5 mL in human) and larger lens (~8 mm in rabbit versus ~4 mm in human). These factors present an increased risk of the implants coming into contact with the soft tissues in the posterior segment of the eye during injection, and potentially post-injection. Special consideration was needed when designing the study to ensure that any lesions resulting from the dosing procedure could be identified, monitored throughout the study, and ultimately differentiated from API-related effects.

Study Details

<table>
<tr><td>Animal model: DB rabbits</td><td rowspan="3">General observations: clinical signs, body weights, food consumption</td></tr>
<tr><td>Duration of study: 1.5 years</td></tr>
<tr><td>No. of animals: 7M/7F per cohort</td></tr>
<tr><td>Dose route: intravitreal implantation</td><td rowspan="2">Ocular measurements/observations: ophthalmic examination, intraocular pressure, electroretinogram, fundus photography, ocular histopathology</td></tr>
<tr><td>Dose regimen: single intravitreal delivery to both eyes on Day 1</td></tr>
</table>

Study Purpose

The objective of the study was to assess the toxicity and toxicokinetics of the sponsor's intravitreal implants for a period of up to 1.5 years following a placement of the implants in the vitreous space of both eyes in DB rabbits.

Methods

Animals were dosed by intravitreal injection using proprietary injectors provided by the Sponsor. All eyes were dosed once at the start of the study according to the table below.

GROUP	TREATMENT	# OF IMPLANTS PER EYE
Control	Placebo implant	2
Test article low-dose	Test implant	2
Test article mid-dose	Test implant	3
Test article mid-dose	Test implant	4
Test article high-dose	Test implant	6

All test implants contained the same mg amount of API. Implants were delivered with a single injection (control and low dose) or two successive injections (mid- and high-dose).

Standard safety observations and measurements were performed over the course of the study, including detailed clinical observations, body weights, food consumption, and clinical pathology.

Ocular assessments were done prior to injection, once during the week following injection, approximately once a month during the first year, and then approximately once every two months during the final six months of the study.

Ocular assessments included fundus imaging (RetCam Shuttle), intraocular pressure (Reichert TonoPen), ophthalmology examination, and electroretinography. Ophthalmology examinations were performed by a board-certified veterinary ophthalmologist, and included examination of the anterior segment with the aid of a slit lamp and examination of the fundus using an indirect ophthalmoscope and an aspheric condensing lens.

Blood samples were collected periodically over the course of 18 months to assess systemic exposure.

Animals were euthanized at approximately six months and 18 months following placement of the implants. Complete necropsies were conducted, and standard organ weights were recorded. The eyes were collected and preserved en bloc for histopathology evaluation. The eyes were then sectioned at three levels, processed to slide, and stained with hematoxylin and eosin. Slides were read by a board-certified veterinary pathologist.

Results

Although minimal systemic exposure to the API was detected in test group animals, there was no evidence of systemic effects.

Non-adverse findings were noted for the eyes during the in-life phase.

The pathologist noted microscopic findings in the vitreous, lens and retina of control, and test eyes. All vitreous findings were deemed non-adverse due to limited severity. Microscopic observations noted for the lens were considered injection procedure-related and adverse. Microscopic findings in the retina were considered to be injection procedure-related, some adverse and some not.

Electroretinography revealed waveform abnormalities in some eyes that received six implants, including reduced b-wave positivity in the dark-adapted response reduced light-adapted response.

The general appearance of the implants was observed by indirect ophthalmoscopy and fundus imaging. The implants remained intact over the course of the study. A gradual decrease in coloration of the API-containing implants was observed and was attributed to depletion of the test drug.

Conclusion

The technical and scientific challenges associated with the placement of multiple implants in the relatively small vitreous space of DB rabbits required specialized instruments and qualified experts in the fields of veterinary ophthalmology, veterinary pathology, and electroretinography. The combined expertise of our team, familiarity with the test species, and commitment to making the review and interpretation of the data a collaborative effort, allowed for us to differentiate between effects associated with the injection procedure, the API, and/or the implant itself. These distinctions can be critical to acceptance of the study results by regulatory agencies.

BIOANALYSIS

The accurate collection and handling of ocular samples requires highly trained, experienced scientists. Sampling is an essential part of the analytical process; close communication and collaboration between the bioanalytical and *in vivo* scientists is crucial.

The structure and function of the eye, PK and drug disposition, ocular safety evaluation, and the ocular dynamics of various species are critical considerations when developing a bioanalytical assay. Most ocular tissues can only be harvested at terminal sampling, and cross-contamination must be carefully managed.

Tear (lacrimal fluid) is the only easily accessible matrix for non-invasive sampling in humans, and can be used for therapeutic drug monitoring. Tear can be collected by different methods such as Schirmer test strips, filter paper, cellulose sponges, and graduated capillary (glass or plastic).

The use of appropriate sample collection procedures determines the quality of the final results. Consideration for paper tear strips is that it is difficult to measure the exact volume of tears that permeate the strip, and recovery may not be complete. They may also cause eye irritation and promote tear secretion, which dilutes and falsifies the drug concentration. Direct sampling with glass or polypropylene capillaries provides accurate low-volume samples without the potential issue of incomplete extraction of the analyte from the support material.

Tissues are snap frozen and typically stored at -80 °C. Additional measures to ensure stability, such as light protection or the addition of stabilizers, are applied as needed. Weighing of tissues just after collection saves an additional step during bioanalysis, and can negate sample losses and potential stability issues.

Homogenization and Sample Preparation

Ocular bioanalysis faces the challenge of matrix heterogeneity–tissues can be liquid, soft, or hard/solid. One of the most important steps for successful tissue bioanalysis is proper homogenization of tissues via chemical, mechanical, or enzymatic processing. The tissue type and the analyte's physicochemical properties will determine the most suitable technique. For example, dilution of solid tissue is necessary for homogenization and this is usually performed in a suitable media. In most instances, mechanical homogenization through a bead-beating process is required. Optimization of this process includes the weight-to-volume ratio of tissue to media, the choice of bead material (ceramic versus stainless-steel), bead size and shape (smooth versus serrated), number of beads added to the sample, and the duration of homogenization. As homogenization of solid tissue by bead-beating is an exothermic process, it is often necessary to incorporate a chilling process between bead-

beating cycles in order to moderate sample temperature, thereby ensuring analyte stability. It is also critical to evaluate the impact of bead material to verify a lack of reactivity (e.g., oxidation of analyte with stainless steel beads or non-specific binding). The use of stable isotope labeled internal standard (SIL-IS) is always recommended for mass spectrometric analysis, and in the case of tissue analysis is best added to the homogenate prior to sample extraction. In this manner, the use of peak-area ratio measurement compensates for the inherent variability in analyte recovery, pipette aliquoting, LC injection, and fluctuation in MS ionization, the latter caused by donor-to-donor dependent matrix effects. Should a SIL-IS be unavailable, a structurally related analog which ideally co-elutes with its target analyte should be selected.

Regardless of the ocular matrix composition, sample cleanup by liquid-liquid extraction (LLE), supported-liquid extraction (SLE), or solid-phase extraction (SPE) may be required. The choice of sample preparation procedure is often dictated by the targeted lower-limit of quantitation (LOQ), the requirement for extract cleanliness, and the concomitant need to eliminate interference that may impact assay selectivity and consistency in analyte response (i.e., matrix effect). When not confronted by low detection limits or matrix interference, protein precipitation can be sufficient. Tears or aqueous humor (AqH) rarely require a complicated sample preparation process, and usually dilution of the sample followed by direct analysis suffices.

Analytical Challenges

- **Stability**

  Samples are commonly snap frozen upon collection and stored at -80 °C due to the difficulty in evaluating, *a priori,* the stability of analyte when distributed throughout intact tissue (i.e., scientific consensus is that intact tissues cannot be homogeneously spiked with analyte, and therefore tissue homogenate is fortified to determine stability). If previous knowledge exists regarding analyte stability in wet matrices (e.g., plasma, AqH), measures such as handling on ice, addition of stabilizers, and light protection can be leveraged to minimize potential degradation.

- **Nonspecific Binding (NSB)**

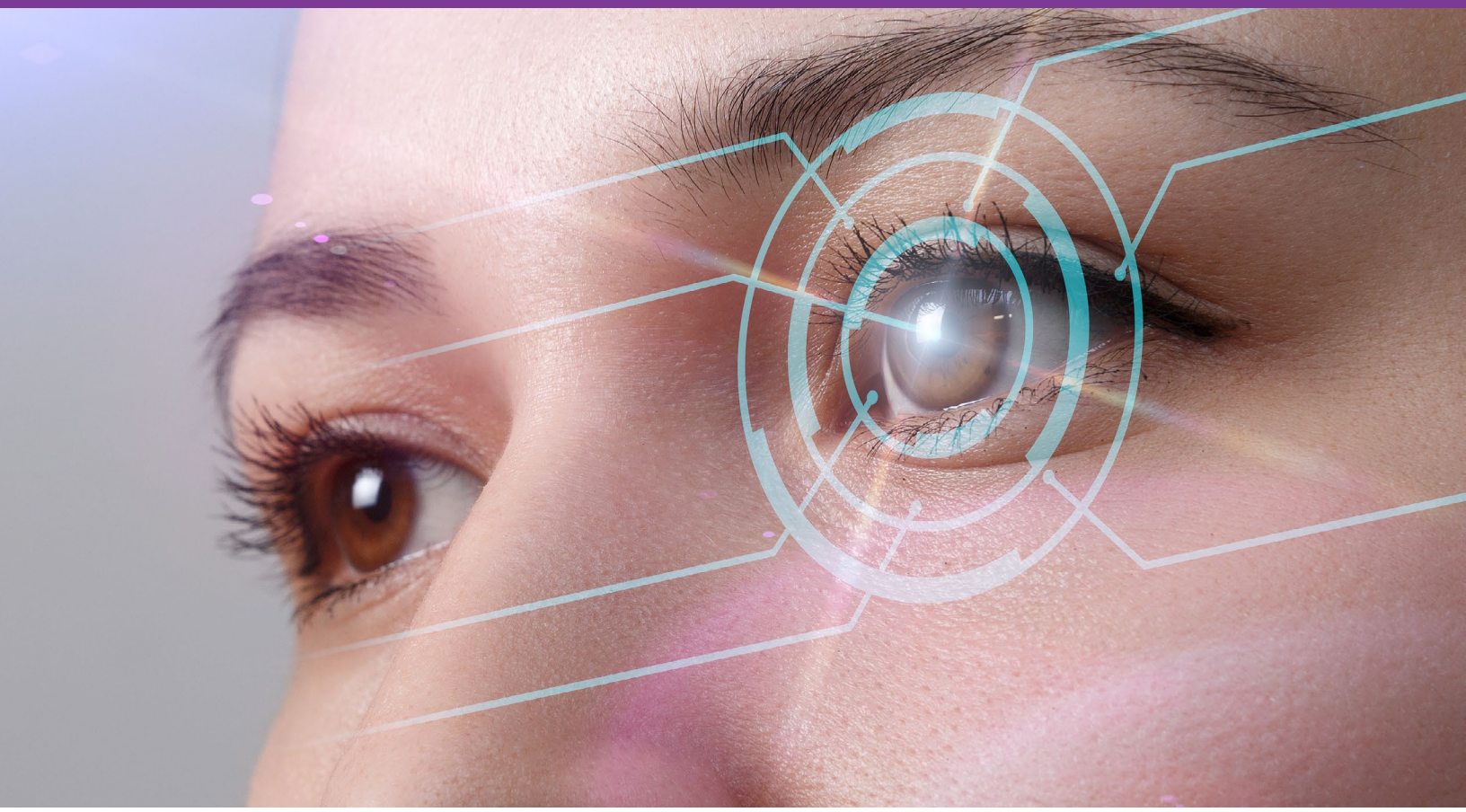
  In many instances, ocular drugs are designed to specifically bind to tissue to facilitate prolonged exposure, or are introduced as a slow release formulation. These molecules can exhibit poor aqueous solubility and have a propensity to undergo NSB to the collection vessels when sampling AqH or vitreous humor (VH). Downstream processing losses of analyte in pipette tips or 96-well plates can cause variable results and nonlinear calibration curves, the impact most often biased towards lower analyte concentration. Consequently, NSB is evaluated early in the method development process and if found, sample processing recommendations such as the requirement for addition of an anti-adsorptive agent, at an optimal volume ratio, are made. Successful implementation of this approach relies upon an accurate recording of the collected sample volume, measured by the collection device or calculated using a combination of specific gravity and sample weight, the latter requiring a determination of empty vessel weight prior to collection. In the case of ocular tissues, NSB is less problematic due to pacification of vessel binding surfaces by endogenous protein.

Sourcing Control Matrix

For *in vivo* studies requiring terminal sampling, the study design is carefully considered to minimize the number of animals sacrificed. The sourcing of adequate amounts of control matrices can be challenging, particularly for small animals, due to limited matrix volume or low tissue weight. Using surrogate or synthetic matrices, and taking a tiered approach to method validation, fit-for-purpose methods can address the issue. Obtaining human ocular matrices is possible only in exceptional cases, and when unavailable, a control matrix from a nonclinical species may be necessary as the biological surrogate.

For example, human AqH is considered a rare matrix due to poor availability and prohibitive cost. Consequently, artificial AqH can be used as a cost-effective and abundant non-biological surrogate for calibrants and quality controls (QCs), and AqH from an appropriate nonclinical species can be used to prepare biological QCs representative of study samples. Equivalency of accuracy and precision must be demonstrated within acceptance criteria for QCs prepared in both biological and artificial AqH surrogates when measured against a calibration curve derived from artificial AqH.

Matrix effects and internal standard behavior are critical considerations when selecting an appropriate surrogate, as they should emulate those attributes of incurred samples, otherwise variances can be significant. One commonly employed strategy is to use plasma as a surrogate, since in most cases these assays are well understood and their performance is previously validated. In this approach, an aliquot of tissue homogenate can be fortified in control plasma and these QC samples then evaluated against calibrants prepared directly in control plasma to determine equivalency.



PHASE I CLINICAL RESEARCH

Phase I clinical trials are designed to test the safety, side effects, best dose, and timing of an NCE destined for human health treatment. Phase I trials also can be used to determine the most effective route of administration, and important pharmacokinetic and pharmacodynamic (PK/PD) parameters of the NCE.

Ophthalmic trials require particular attention to participant selection where pre-existing conditions that could theoretically be caused by the NCE are excluded prior to the study.

Ophthalmic procedures require specialized equipment and highly trained clinical personnel. There are several different routes of administration for ocular therapies, described in more detail above, each requiring great care when used in Phase I trials. Tight integration between the techniques and analysis used in the preclinical laboratory, the study clinic, and the ophthalmology clinic is essential for a safe and efficient study that can lead to NCE progression to a Phase II study.

The most common methodologies for ophthalmic drug development are:

- topical administration
- systemic administration
- intravitreal injections
- intraocular implants
- subretinal injections
- suprachoroidal injections

In conducting Phase I clinical trials, the approach to each patient is different than for a standard ophthalmology examination. Advanced technology and standardized protocols must be used to obtain the quality of data sufficient for early detection of adverse events, and to obtain regulatory approval of a medication.

In addition to standard diagnostic devices, Altasciences has access to the following experience and tools in the listed areas:

- Coordination of ophthalmic testing with intensive PK and PD clinical laboratory testing
- Close coordination between ophthalmic and general medical treatments, evaluations, and testing (i.e., intravenous infusions, ERGs, radiological testing, and clinical laboratory testing)
- Clinical trial design, including genomic trials
- Best-corrected visual acuity (BCVA) using established Early Treatment of Diabetic Retinopathy Study (ETDRS) protocols
  - Provides standardized, quantitative evaluation of visual function that is amenable to biostatistical analysis
- Slit-lamp examinations
  - Allows microscopic analysis of the eyelids and front of the eye
- Slit-lamp photography
  - Permits documentation of findings on a slit-lamp examination

- Standardized testing for dry eye or corneal toxicity
  - Quantified testing for clinical findings of toxicity and dry eye.
- IOP measurement
  - Allows investigators to evaluate if a medication (such as many glucocorticoids) causes a change in eye pressure or glaucoma.
- Standardized installation of eye drops
  - Standardized techniques and training to administer eye drops is essential to avoid missed doses or excessive treatment.
- Gonioscopy
  - Permits the ophthalmologist to evaluate the study participants to rule out a risk of angle closure, which can cause an attack of elevated eye pressure and possible blindness.
- Fundus photography
  - A digital, quantitative method to document baseline findings and changes in the retina.
- Ocular coherence tomography (OCT) of both the anterior and posterior segment
  - Allows creation of a high-resolution, three-dimensional image of the optic nerve, the macula and other eye structures.
- Ocular coherence tomography angiography (OCTA)
  - Permits the direct imaging of retinal vessels in the retina and optic nerve without the use of contrast agents.
- Fluorescein angiography
  - Permits the direct imaging of retinal vessels and leakage of these vessels in the retina and optic nerve with the use of the contrast agent fluorescein.
- Multifocal electroretinography (mfERG)
  - A quantitative evaluation of the function of the macula taken by evaluating changes in voltage between the cornea and the skin using a contact lens.
- B-scan ultrasonography
  - Evaluation of the structure of the back of the eye including evaluating the thickness of the different layers of the eye.

CLINICAL CASE STUDY

A Phase I, double-masked, vehicle-controlled study to assess safety, tolerability, and pharmacokinetics of ascending doses of palovarotene ophthalmic solution in healthy adults

William J Foster,[1] James M Roach,[2] Andrew L Strahs[2]

[1]Altasciences, Montréal, Canada; [2]Ipsen, Cambridge, MA, U.S.A.

Purpose

An ophthalmic solution formulation of palovarotene (POS), a selective retinoic acid receptor γ agonist, is under investigation for the treatment of dry eye disease (DED). The purpose of this study was to determine the ocular and systemic safety, tolerability, and pharmacokinetics of ascending doses of POS in healthy adults.

Methods

This was a single-center, randomized, double-masked, vehicle-controlled Phase I study in healthy adults. Participants were randomized 3:1 to receive either POS (at 0.025, 0.05 or 0.10 mg/mL) or vehicle (placebo-to-match POS). Six cohorts of eight participants were planned for evaluation (six participants in the POS group and two in the vehicle group); three cohorts were each administered treatment once daily (QD) or twice daily (BID) for seven consecutive days. Escalation to the next dose required Review Committee approval. Healthy adults, 18 to 55 years of age, were eligible for this study. Safety was assessed by physical examinations, vital signs, ECGs, clinical laboratory parameters, ocular assessments, adverse events (AEs), and treatment emergent ocular adverse events (TEOAEs). Blood samples for PK assessments of POS were collected from study participants prior to and following dose administration.

Results

36 participants were randomized to POS and 12 to vehicle. Overall, 89 TEOAEs were reported by 22 participants (61%) receiving POS and 10 TEOAEs were reported by five participants (42%) receiving vehicle. Erythema, irritation and skin dryness of the eyelid were the most common TEOAEs in participants receiving POS. Overall, the incidence of TEOAEs and eyelid-related findings in participants treated with POS increased with ascending dose and frequency compared with participants treated with vehicle. All TEOAEs were mild (96.6%) or moderate (3.4%) and resolved without sequelae. There were no serious AEs. Similar PK profiles were observed for the QD and BID regimens following multiple ascending doses of POS. No meaningful difference was observed between the PK profile of POS following the AM and the PM doses during BID treatment.

Conclusion

The administration of POS was generally well tolerated at doses up to and including 0.10 mg/mL BID. These data support further investigation of the safety and efficacy of POS in patients with DED.

PHASE II TO COMMERCIALIZATION

The complexity and challenges of bringing ophthalmic therapeutics to market can be mitigated by maintaining long-term relationships with CRO/CDMO partners as the product advances through the development phases.

Altasciences' integrated capabilities can support your program from day one to market. We can start your project off with regulatory and scientific guidance, to ensure your program meets all regulatory requirements and is scientifically and logistically feasible. Then, we can develop your small molecule formulation and produce your clinical supply, and scale up to commercialization, applying learnings from each phase of development. We also analyze your preclinical samples and run the assays throughout your program, for both large and small molecule. And all along the way, we remain your sole data management partner.

Consistency, communication, ease of data transfer, less handoffs and fewer logistical challenges of negotiating contracts, managing NDAs, etc., are all benefits of working with a single, integrated end-to-end CRO/CDMO partner. Maximizing efficiency and optimizing drug development, to ultimately bring better products to market, faster.

PRECLINICAL SAFETY TESTING

- 50 years of experience — no study ever rejected for reasons of design, conduct, or data integrity
- Broad solutions offering across dosing routes and specialized techniques
- On-site Diplomate, American College of Veterinary Ophthalmologists (DACVO)
- Significant investment in specialized equipment like OCT and Retcam

FORMULATION, MANUFACTURING, AND ANALYTICAL SERVICES

- Seamless transition from proof-of-concept formulations to clinical manufacturing
- Potent compounds and controlled substances
- Class C Manufacturing suites for development and clinical/commercial batches
- Flexible filling options, including vials, droppers, and custom containers
- Scale options from small batches up to 400L
- Milling capabilities for micro-and nanosuspension products
- Expert analytical support for method development, validation, and ICH stability testing

REGULATORY AND SCIENTIFIC AFFAIRS

CLINICAL RESEARCH SERVICES

- In-house ophthalmologist with over 20 years of experience
- Three North American inpatient units (from coast to coast) with over 500 beds — fully equipped inpatient and outpatient capabilities
- Robust network of ophthalmology sites in close proximity to our clinics
- FIH to Phase IIa focused, more than 40 ophthalmology trials completed
- Database of over 400K participants for healthy normal and patient recruitment

BIOANALYTICAL SERVICES

- Strong, in-house ocular bioanalytical scientific expertise
- State-of the-art instrumentation to achieve low limits of quantitation for systemic exposure
- Expertise working with rare and limited matrices such as tears

ALTASCIENCES' RESOURCES

Fact Sheet

Ophthalmology

Webinars

Terminal Sterilization

Develoment of nanosuspensions

INTEGRATED SOLUTION

Webpages

Proactive Drug Development

A.T.L.A.S. Customized End to End Approach

eBook

Integrated Solution for Preclinical to Clinical Drug Development

REFERENCE

1 https://www.grandviewresearch.com/industry-analysis/ophthalmic-therapeutics-drug-market

2 Ali H, Khan S, York P et al. A stable hydrocortisone nanosuspension for improved dissolution: Preparation, characterization and *in vitro* evaluation *Pak. J. Pharm. Sci.*, 2017;30(5):1635-1643

3 Fiscella RG, Jensen M, Van Dyck G. Generic Prednisolone Suspension Substitution. *Arch Ophthalmol*. 1998;116(5):703

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.