



ACUSTREAM™: BRINGING TOPICAL OPHTHALMIC DRUG DELIVERY INTO THE MODERN ERA

In this article, Peter Noymer, PhD, Chief Executive Officer, Ehud Ivri, Chief Technology Officer and Co-founder, Reynaldo Quintana, Vice-President of Engineering, and Mark Blumenkranz, MD, Executive Chairman and Co-founder, introduce AcuStream, a novel device for next-generation delivery of topical ophthalmic delivery via an aim-assisted stream.

INTRODUCTION

Virtually all topically administered ocular therapies are delivered by a standard eyedropper, requiring the patient to tilt their head back and administer a prescribed number of drops into their eye one or more times per day. This method is woefully out of date, with:

- More than 90% of patients dosing improperly
- 24% of eyedrop bottles being contaminated¹
- 30% of patients who think they have good technique actually missing the eye.²

This is not modern medicine.

Standard eyedroppers also end up delivering a dose four or five times larger than the tear film of the eye can retain, meaning that more drug than necessary is being dosed compared with what is actually required to treat a given condition. The majority of the delivered formulation is often washed out of the eye or even misses the eye entirely because of poor delivery technique. This overdosing can also cause systemic adverse events if the drug enters the systemic circulation in high enough quantities. For example, the beta blocker timolol, used in the treatment of glaucoma, has been documented to have potential cardiac or pulmonary complications

in high risk populations if it reaches high enough systemic concentrations after conventional topical administration. And any excess drug product remaining in the eye may lead to local adverse events. For example, prostaglandins can cause conjunctival hyperaemia, increased pigmentation of the iris, or abnormal eyelash growth.

Dosing five times more than the therapeutic dose is also wasteful of drug product. In mass markets, with the wastage multiplied across millions of doses per year, the cumulative cost on the healthcare system can grow very quickly, even for lower-cost APIs. Clearly, a system that could administer much less active ingredient and only what is needed both more accurately and comfortably would be highly desirable from both a clinical and an industrial point of view.

Patients have demonstrable difficulty properly using traditional eyedroppers. These difficulties lead to deficiencies in both compliance, whereby patients administer

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Figure 1: Kedalion’s AcuStream device for delivering topical front-of-the-eye ophthalmic medication.

the wrong number of drops (exacerbating the existing issue of too much drug product being delivered) or fail to target the eye properly, and adherence, meaning patients are put off continuing their therapy due to discomfort, adverse events, inconvenience or other issues.

There is a clear, unmet need in the ophthalmology market for an improved, efficient modern delivery system.

ACUSTREAM, THE NEXT STAGE OF TOPICAL OPHTHALMIC DELIVERY

Kedalion Therapeutics is a venture-backed, clinical-stage ophthalmology company based in Menlo Park, CA, US. Kedalion aims to meet this unmet need in topical ophthalmic drug delivery and to transform the topical ophthalmology market with its proprietary AcuStream™ delivery system for topical ocular treatments (Figure 1). AcuStream is a proprietary device for easy, accurate and precise dosing, which is achieved using a novel dispensing mechanism. AcuStream administers a topical formulation directly to the surface of the eye without patients tilting their heads back and with a proprietary aiming mechanism to improve accuracy of delivery. Patients hold the device in front of their eye rather than above it, greatly increasing not only comfort and ease-of-use but crucially also increasing dose precision and accuracy with the novel aiming and dispensing mechanisms.

Human factors design played a significant role in the creation of AcuStream. A major contributor to the difficulties in ensuring patient compliance with topical ophthalmic treatments is the discomfort patients experience with traditional eyedrops, having to crane their heads back and to try to line up the dropper directly above their eye. In addition, an exaggerated blink reflex and lid spasm could block the administration of the drop or cause the medication to be

ejected from the surface of the eye. The proprietary aiming and delivery mechanisms in AcuStream allow straightforward dosing, meaning that patients apply their topical medication while looking directly forward, a more natural position that engenders greater accuracy and comfort, and therefore better compliance (Figure 2). The aiming technology makes it easy for patients to ensure that their ophthalmic medication is delivered directly to the eye, and the dispensing technology ensures that the proper dose is administered reproducibly.

This novel approach can also improve adherence. Because the dose is reliably and precisely delivered, AcuStream delivers less drug to achieve the same effect, meaning that there is less drug wasted and that drugs delivered by AcuStream could result in fewer adverse events than standard eyedroppers. This, combined

with enhanced comfort and ease-of-use, means that patients may have more incentive to adhere to an AcuStream treatment regimen compared with standard eyedroppers.

This is especially important for a chronic condition such as glaucoma, for example. When it comes to treating glaucoma, healthcare providers have a broad array of increasingly invasive treatments for managing intraocular pressure (IOP), starting with simple topical drug formulations before moving up to stents and possibly even surgery. Therefore, if a patient has compliance and adherence issues with their initial topical treatments, it increases the probability that IOP will not be well-managed and that more drops would have to be prescribed to try to manage IOP before moving on to increasingly invasive, surgical treatments.



Figure 2: AcuStream delivers medication directly to the eye in a stream with the patient looking directly forward, assisted by a proprietary aim-assisting mechanism.

AcuStream’s clear benefits position it for success in the topical ophthalmic market, in the treatment of conditions such as glaucoma, dry eye, uveitis, allergic disease and infections. Additionally, the regulatory pathway to approval for AcuStream combined with approved drugs can follow streamlined processes such as the US FDA’s 505(b)(2) approval pathway. Because of its novel design and mode of use, AcuStream is not only applicable for optimal delivery of existing therapies as differentiated products or for lifecycle management, but it could also change the landscape for new molecular entities (NMEs) in the topical ophthalmic space by creating a new paradigm for dosing and treatment.

AcuStream’s precision dispensing mechanism uses an IP-protected architecture and is compatible with existing pharmaceutical manufacturing processes to minimise disruption and facilitate easy adoption as the topical ophthalmic delivery device of choice. Underlying the novel delivery system, AcuStream uses traditional drug container materials manufactured using standard aseptic fill-finish processes, thus making it easier to adopt AcuStream and integrate it into existing low-cost industrialisation processes.

Promising Phase I Clinical Trial Results

In 2017, Kedalion conducted two clinical trials comparing AcuStream with standard eyedroppers.

The first trial measured pupil dilation following administration of a tropicamide-phenylephrine combination formulation (1% tropicamide solution combined with 2.5% phenylephrine solution). The study comprised 40 doses in 20 patients, each treated using a single AcuStream dose in one eye and a single standard eyedropper dose in the other eye (randomised for left eye and right eye). As shown in Figure 3, AcuStream achieved a statistically similar dilation effect while using a 70% lower dose. AcuStream was also shown to be 45% more comfortable and resulted in 35% fewer adverse events.

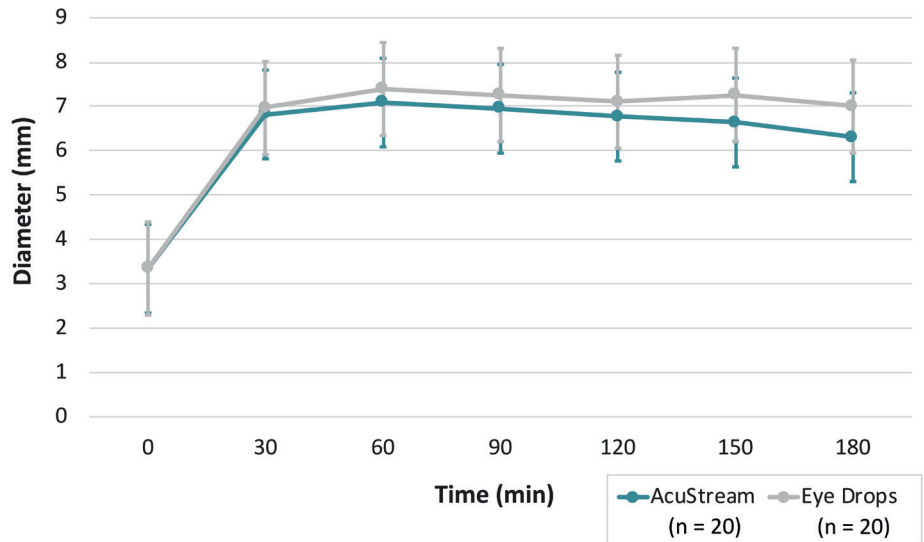


Figure 3: Phase I dilation results – AcuStream versus standard eyedropper tropicamide-phenylephrine.

The other trial measured IOP in glaucoma patients following administration of latanoprost. The study comprised 36 doses in 18 patients with ocular hypertension or glaucoma already under topical oculohypotensive therapy. Patients first underwent a washout of existing topical medication for a minimum of one month and then were randomised to be treated using either a single AcuStream dose in both eyes of latanoprost 0.005%

or a single standard eyedropper dose in both eyes of latanoprost 0.005%. As shown in Figure 4, the AcuStream cohort achieved a statistically similar effect in IOP reduction while using a 70% lower dose compared with the eyedropper cohort.

Both trials very clearly demonstrated proof-of-concept for the effectiveness and improved comfort, convenience and safety of the AcuStream delivery system.

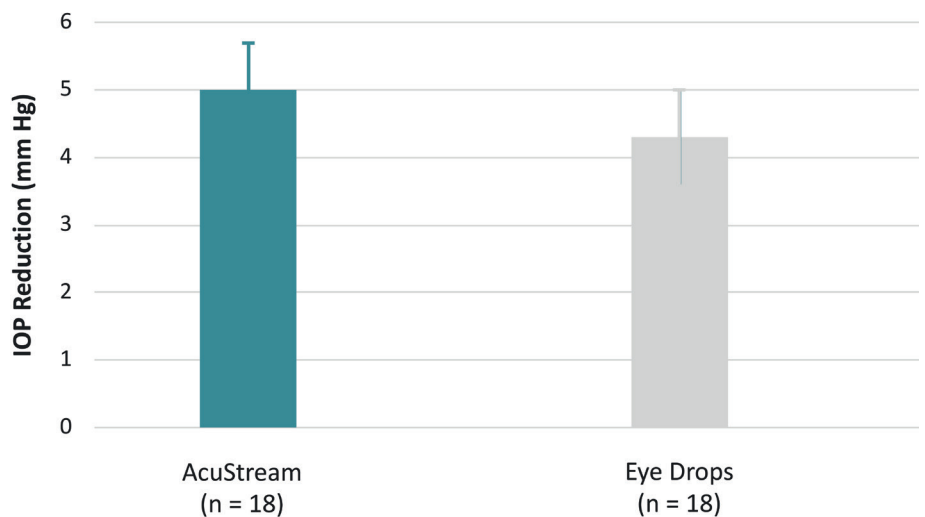


Figure 4: Phase I glaucoma results – AcuStream versus standard eyedropper latanoprost.



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WHERE TO NEXT?

Since being founded in 2015, Kedalion Therapeutics has progressed rapidly to become a clinical-stage topical ophthalmic product company, having completed two successful Phase I trials. Phase II studies are planned for mid-2019 and initial marketing applications and approvals are anticipated in the 2021/22 timeframe.

In addition to the pipeline of drug products, Kedalion anticipates being able to offer different platform features as

needed to meet patient needs in different therapeutic areas. Such features are expected to include connectivity elements to support digital health initiatives as well

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as container closure system that could allow preservative free formulations to be provided in a multi dose format.

AcuStream is strongly IP-protected with patents extending out to 2032 and beyond. Kedalion is establishing a proprietary product pipeline based on AcuStream. In addition, AcuStream presents the opportunity for partnerships with the means to expand the ability to offer patients a comfortable, convenient and effective ophthalmic delivery system fit for the modern age. AcuStream has the potential not only to make topical ophthalmic medicines stand out from competitors, but also to enhance them by making them more patient friendly, increasing adherence and compliance, and additionally reducing drug product wastage.

Importantly, in addition to the prescription pharmaceutical market, AcuStream also has the potential to move into over-the-counter (OTC) ophthalmics market. Its distinctive novel delivery method, patient-centric design and fast regulatory pathway make it an ideal candidate for OTC medications.

CONCLUSION

Kedalion's AcuStream device is set to revolutionise topical ophthalmic delivery across multiple indications. The patient-friendly device delivers medication accurately and precisely in a straightforward stream that is easy to aim and matches the efficacy of standard eyedroppers but using up to 80% less drug product. With a streamlined route to regulatory approval available for existing drugs, very low cost-of-goods, compatibility with existing pharma manufacturing processes, and its ability to distinguish itself in a market ripe for innovation, AcuStream offers a clinically and commercially attractive opportunity for a differentiated ophthalmic product portfolio.

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ABOUT THE AUTHORS

Peter Noymer is Chief Executive Officer of Kedalion Therapeutics and has more than 20 years of experience in research, development and commercialisation of pharmaceutical products with novel delivery technologies. Before joining Kedalion, he was Chief Operating Officer at SteadyMed Therapeutics, focused on developing novel products with the PatchPump™ technology. Earlier, Peter was Vice-President of Product R&D at Alexza Pharmaceuticals, where, during his time there, the company obtained US and EU approval for Adasuve®(loxapine), the first inhalable treatment for agitation associated with schizophrenia or bipolar I disorder. Prior to Alexza, Dr Noymer held various management positions at Aradigm Corporation. He received MS and PhD degrees in engineering from MIT, and a BS degree in engineering from Princeton University.

Ehud Ivri is Kedalion's Chief Technology Officer and Co-founder. He is an electro-mechanical engineer specialising in microfluidics and piezo-electronics, focused mainly in the field of drug delivery. He holds over 40 patents related to medical devices and drug delivery systems. Mr Ivri's work in the medical device field began with his founding of Aerogen, now a leading producer of nebulisers for inhalable drug delivery. More recently, he developed a new micro-dispensing technology for the production of DNA micro-arrays that was licensed to BioDot. Mr Ivri holds an MS in Mechanical Engineering from the Technion-Israel Institute of Technology.

Reynaldo Quintana is Kedalion's Vice-President of Engineering. Prior to Kedalion, he was Senior Director of Global Engineering at Fontem Ventures, and also led device development at Alexza Pharmaceuticals. Mr Quintana also held management positions with NJOY, ZOLL Medical, Aerogen and IDEO, and consulted to Sunovion Pharmaceuticals, Genentech and Elevation Pharmaceuticals. He is an inventor or co-inventor on 18 biomedical patents. He received a BS in Mechanical Engineering from the University of Maryland, a BS in Physics from Frostburg State University and an MS in Biomedical Engineering from The Catholic University of America.

Mark Blumenkranz is Kedalion's Executive Chairman and Co-founder, a noted serial entrepreneur and the Managing Director of Lagunita Biosciences. Dr Blumenkranz is also the HJ Smead Professor Emeritus of Ophthalmology at Stanford University and was departmental Chairman from 1997 to 2015 and the founding director of the Byers Eye Institute. He was a Founder and Director of Macusight, Peak Surgical, Optimedica Corporation, Adverum Biotechnologies, Oculve and Digsight Corporation (now Verana Health). He has also served on the Boards of Directors of a number of other private and publicly traded ophthalmic drug and medical device companies including Oculex Pharmaceuticals, OIS, Midlabs, Presbia, and Beaver-Visitec (BVI Inc). He completed the Stanford Executive Program in the Graduate School of Business in 2004 and received his undergraduate, Masters in Biochemical Pharmacology, and MD from Brown University (AOA), where he is a Fellow of the Corporation and Immediate Past Chair of the Medical School Committee.