



Bimatoprost Implant: First Approval

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Abstract

Bimatoprost implant (Durysta™), developed by Allergan, is a sustained-release drug delivery system containing bimatoprost, a prostaglandin analogue with ocular hypotensive activity. The implant, administered intracamerally, involves the use of a biodegradable, solid polymer drug delivery system for slow, sustained drug release, designed to lower intraocular pressure (IOP) over a 4- to 6-months period. In March 2020, bimatoprost implant received its first approval, in the USA, for use to reduce IOP in patients with open angle glaucoma (OAG) or ocular hypertension (OHT). Allergan's clinical development programme for bimatoprost implant is ongoing. This article summarizes the milestones in the development of bimatoprost implant leading to this first approval for use in the reduction of IOP in patients with OAG or OHT.

Bimatoprost Implant (Durysta™): Key Points

A biodegradable sustained-release intracameral implant containing the prostaglandin analogue bimatoprost

Developed by Allergan, bimatoprost implant received its first approval on 04 March 2020, in the USA

Approved for use to reduce IOP in patients with open angle glaucoma or ocular hypertension

1 Introduction

Open-angle glaucoma (OAG) is a chronic and progressive eye disorder that is characterized by optic nerve damage and is commonly associated with elevated intraocular pressure

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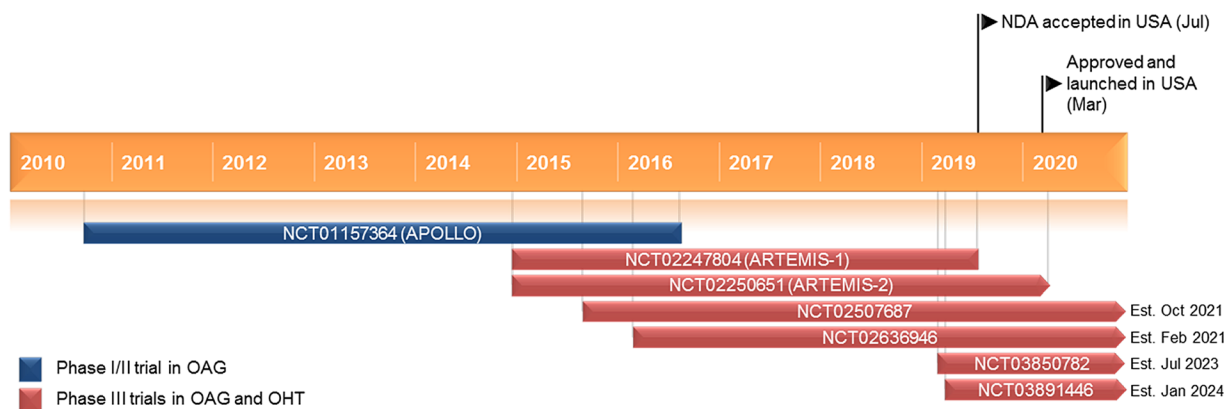
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(IOP) [1, 2]. In OAG, disease progression leads to irreversible visual field loss and, if untreated, can result in blindness. Management of OAG centres around the use of medications, laser trabeculoplasty or surgery (or a combination of the three) to lower IOP with the aim of preventing or slowing vision loss. First-line treatment for OAG usually involves the use of topical IOP-lowering medications, most commonly prostaglandin analogues (e.g. bimatoprost, latanoprost, travoprost). Other classes of topical IOP-lowering medications used for the treatment of OAG include cholinergic agonists (e.g. pilocarpine), β -adrenergic receptor blockers (e.g. timolol), α -adrenergic receptor agonists (e.g. brimonidine) and carbonic anhydrase inhibitors (e.g. brinzolamide) [1, 2].

Although topical medications are generally efficacious in lowering IOP, adherence issues frequently complicate disease management [3–6]. Factors reported to negatively impact adherence to topical IOP-lowering medications include a poor understanding of the disease, poor self-efficacy, difficulty in eye drop administration, forgetfulness, multiple dosing requirements, and adverse events [5]. To help overcome or circumvent adherence issues, sustained drug delivery systems have been investigated for the treatment of OAG and ocular hypertension (OHT) [7]. Bimatoprost implant (Durysta™), a bimatoprost sustained-release device developed by Allergan, received its first approval on 04 March 2020, in the USA, for use to reduce IOP in patients with OAG or OHT [8, 9]. The implant, approved for a single intracameral administration, consists of a biodegradable, solid polymer, sustained-release drug delivery



Key milestones in the development of bimatoprost implant for OAG and OHT. *NDA* New Drug Application, *OAG* open-angle glaucoma, *OHT* ocular hypertension

system containing a 10- μ g bimatoprost dose [9]. A New Drug Application for bimatoprost implant for use in the treatment of OAG and/or OHT, supported by the findings of the phase III ARTEMIS-1 and ARTEMIS-2 clinical trials (Sect. 2.4.1), was accepted by the US FDA in July 2019 [10].

1.1 Company Agreements

Bimatoprost implant was originated and developed by Allergan. In March 2015, Allergan was acquired by Actavis [11]. Subsequently, in June 2015, Actavis changed its name to Allergan [12]. In May 2020, Allergan was acquired by, and merged into, AbbVie [13].

2 Scientific Summary

The US FDA-approved bimatoprost implant product is a sterile intracameral implant that consists of a 10- μ g dose of bimatoprost held within a rod-shaped biodegradable solid polymer drug delivery system based on Allergan's Novadur[®] platform [9, 14]. For the bimatoprost implant, the Novadur platform was modified to release bimatoprost with non-pulsatile, steady-state drug release [14]. The

polymer drug delivery system in the bimatoprost implant consists of poly (D,L-lactide), poly (D,L-lactide-co-glycolide), poly (D,L-lactide) acid end, and polyethylene glycol 3350 [9].

2.1 Drug Delivery

For administration, bimatoprost implant is supplied preloaded in a single-use applicator to facilitate injection directly into the anterior chamber of the eye [9]. With intracameral administration, the implant is designed to target drug delivery directly to the iris-ciliary body, the key site of action of prostaglandin analogue drugs [14]. Once in place, the polymer matrix of the insert slowly degrades (to lactic and glycolic acids), slowly releasing bimatoprost, with the aim to provide an IOP-lowering effect lasting 4–6 months [9, 14]. The intracameral injection procedure must be performed under magnification for clear visualization of the anterior chamber structures and should be carried out using aseptic conditions, with the patient's head in a stabilized position [9]. The eye should not be dilated prior to the procedure. Bimatoprost implant is currently approved for a single intracameral administration [9].

Features and properties of bimatoprost implant

Alternative names	Bimatoprost SR; bimatoprost sustained-release implant; Durysta™
Class	Amides; antiglaucomas; lipids; prostaglandins; small molecules
Mechanism of action	Prostaglandin F2 α receptor agonist
Route of administration	Implantation
Pharmacodynamics	Acts to lower intraocular pressure by increasing outflow of aqueous humour through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional)
Pharmacokinetics	Following administration of bimatoprost implant, the highest concentrations of bimatoprost plus the metabolite bimatoprost acid are found in the iris–ciliary body (based on a study in dogs); minimal systemic exposure
Most common adverse reactions	Conjunctival hyperaemia, foreign body sensation, eye pain, photophobia, conjunctival haemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, headache
ATC codes:	
WHO ATC code	S01E-E03 (Bimatoprost)
EphMRA ATC code	S1E (Miotics and Antiglaucoma Preparations)
Chemical name	(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide

2.2 Pharmacodynamics

Bimatoprost is a synthetic structural analogue of prostaglandin with IOP-lowering activity [9]. The IOP-lowering effect acts to reduce the risk of progressive optic nerve damage and visual field loss that occurs in OAG. In humans, it is believed that bimatoprost acts to lower IOP by increasing outflow of aqueous humour through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional) [9]. In a study in normotensive dogs, intracameral bimatoprost implant was associated with a transient increase in episcleral venous pressure (peaking at day 8) followed by a sustained decrease (mean change from baseline of -2.4 to -3.9 mm Hg over days 29–65) [15]. Furthermore, bimatoprost implant treatment was associated with a sustained dilation of aqueous outflow vessels [15]. In further studies in normotensive dogs, intracameral bimatoprost implant was found to have a dose-dependent IOP-lowering effect that was maintained for ≥ 3 months post administration [16, 17]. Interestingly, a study in normotensive monkeys found that intracameral bimatoprost implant had an IOP-lowering effect that was additive to that achieved

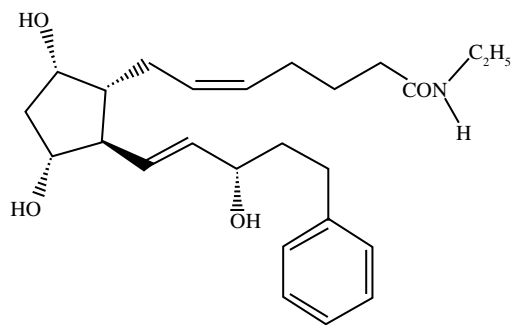
with topical bimatoprost, suggesting that the intracameral implant may have an additional mechanism of action [18].

2.3 Pharmacokinetics

In a study in dogs, peak study drug concentrations in ocular tissues were observed around day 51 after administration of bimatoprost implant $15 \mu\text{g}$ [14]. At this time, 80.5% of the bimatoprost load had been released. By day 80, at which point $> 99\%$ of the bimatoprost load had been released, ocular tissue drug concentrations had declined significantly [14].

Compared with topical bimatoprost, intracameral bimatoprost implant enhances delivery of the study drug to target tissues [14]. Following a single administration of bimatoprost implant $15 \mu\text{g}$ in dogs, highest concentrations of bimatoprost plus the metabolite bimatoprost acid were detected in the iris–ciliary body, the key site of pharmacologic action; drug concentrations in the eyelid margins, periorbital fat and the area centralis of the retina were below the limit of detection. In contrast, following administration of topical bimatoprost 0.03% once daily for 7 days, highest bimatoprost plus bimatoprost acid concentrations were detected in the upper eyelid margin, the lower eyelid margin and the bulbar conjunctiva [14].

Based on clinical data, there is minimal systemic exposure of bimatoprost following a single administration of bimatoprost implant, with the concentrations of bimatoprost and bimatoprost acid below the limits of quantification (0.001 ng/mL and 0.01 ng/mL , respectively) in $\sim 92\%$ and $\sim 99\%$ of patients [9]. The highest bimatoprost concentration detected in any patient was 0.00224 ng/mL [9].



Chemical structure of bimatoprost

Key clinical trials of bimatoprost implant (Allergan)

Identifier	Indication	Phase	Drugs/procedures	Location(s)	Status
ARTEMIS-1; NCT02247804	OAG or OHT	III	Bimatoprost implant; sham implant; timo- lol; timolol vehicle (placebo)	Multinational	Completed
ARTEMIS-2; NCT02250651	OAG or OHT	III	Bimatoprost implant; sham implant; timo- lol; timolol vehicle (placebo)	Multinational	Ongoing
NCT02636946	OAG or OHT	III	Bimatoprost implant; sham implant; SLT; sham SLT	Multinational	Ongoing
NCT02507687	OAG or OHT	III	Bimatoprost implant; sham implant; SLT; sham SLT	Multinational	Ongoing
NCT03850782	OAG or OHT	III	Bimatoprost implant	Multinational	Recruiting
NCT03891446	OAG or OHT	III	Bimatoprost implant	Multinational	Recruiting
NCT04285580	OAG or OHT	III	Bimatoprost implant; bimatoprost ophthal- mic solution	USA	Planned
APOLLO; NCT01157364	OAG	I/II	Bimatoprost implant; bimatoprost ophthal- mic solution	Multinational	Completed

OAG open-angle glaucoma, OHT ocular hypertension, SLT selective laser trabeculoplasty

2.4 Therapeutic Trials

2.4.1 Phase III Trials

Bimatoprost implant reduces IOP with a sustained effect in patients with OAG or OHT based on available data from two randomized, masked, parallel-group, multinational, phase III clinical trials of identical design (ARTEMIS-1 and -2) [19–21].

In each of the trials, patients ($n=594$ and 528) were randomized to receive study eye treatment with bimatoprost implant 10 or 15 μg intracamerally on day 1, week 16 and week 32 or topical timolol 0.5% twice daily [19–21]. Previous IOP-reducing medications were washed out before baseline. The trials each involved a 12-month treatment period with an 8-month extended follow-up. Rescue treatment with topical medication was permitted if the investigator judged that IOP was inadequately controlled [19–21].

Based on pooled data from the two trials, both bimatoprost implant dose strengths were non-inferior to timolol in lowering IOP through week 12 (primary endpoint) [19]. Across the trials, mean reductions in IOP from the baseline of 24.5 mmHg in bimatoprost implant recipients were ~ 7 – 8 mmHg at weeks 2 and 6 and ~ 6 – 7 mmHg at week 12 [9]. From pooled data, responder rates for the achievement of at least 20%, 25%, 30%, 35% and 40%

reduction in IOP from baseline at weeks 2, 6 and 12 were numerically higher in bimatoprost recipients compared with timolol recipients [20]. Currently available data from the trials over a longer timeframe (with data cut-off after the last enrolled patient had completed the week 52 and week 12 visits in ARTEMIS-1 and -2, respectively) show that bimatoprost implant has a durable effect, evidenced by an 82% and 86% probability of bimatoprost implant 10 and 15 μg recipients (pooled across trials) not having added IOP-lowering medication at 360 days after the third bimatoprost implant [21]. Interim 1-year pooled data from the trials also indicate that eyes that had received three bimatoprost implant administrations had less visual field loss than topical timolol-treated eyes [22].

2.4.2 Phase I/II Trial

Further data supporting the efficacy of bimatoprost implant in reducing IOP with a sustained duration of effect are available from a prospective, 24-month, dose-ranging, paired-eye controlled, multinational, phase I/II clinical trial (APOLLO) in 75 adult patients with OAG [23, 24]. Following washout, patients were randomized to receive bimatoprost implant 6, 10, 15 or 20 μg intracamerally in the study eye; the fellow eye was treated with topical bimatoprost 0.03% once daily. Rescue treatment with topical IOP-lowering medication or

a single repeat administration with bimatoprost implant was permitted at the investigator's discretion (with censoring of data) [23, 24].

Bimatoprost implant at all dose strengths tested in the trial effectively reduced IOP with an effect that was broadly similar to the reduction achieved with topical bimatoprost [23, 24]. Mean IOP reduction from baseline (24.5–26.6 mm Hg across groups) in study eyes (primary endpoint) in the bimatoprost implant 6, 10, 15 and 20 µg dose groups, respectively, was 7.2, 7.4, 8.1 and 9.5 mm Hg through week 16 and 7.5, 7.3, 7.3, and 8.9 mm Hg at month 24 compared with mean reductions from baseline (24.1–25.5 mm Hg across groups) in topical bimatoprost-treated pooled fellow eyes of 8.4 mm Hg at week 16 and 8.2 mm Hg at month 24 [23, 24]. Consistent with findings in the phase III trials, there was evidence that bimatoprost implant had a durable effect, with no use of rescue medication/retreatment in 68%, 40% and 28% of pooled study eyes at months 6, 12 and 24, respectively [23]. Additionally, patient-reported outcomes showed that bimatoprost implant was well received, with 82.9% of patients at month 24 reporting that they would be very or extremely likely to have another implant procedure if given the choice, and 88.6% reporting that they would recommend the procedure to someone else with the same eye condition [23].

2.5 Adverse Events

In clinical trials in patients with OAG or OHT, the intracameral bimatoprost implant had acceptable safety and tolerability [9, 19, 20, 23, 24]. The most common adverse reactions in bimatoprost implant recipients in the ARTEMIS-1 and -2 trials were conjunctival hyperaemia (reported in 27% of patients), foreign body sensation, eye pain, photophobia, conjunctival haemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, and iritis (all in 5–10% of patients) [9]. Ocular adverse events observed in clinical trials most typically occurred within 2 days after the implantation procedure and were transient [24]. The most common non-ocular adverse reaction in bimatoprost implant recipients in the phase III trials was headache (reported in 5% of patients) [9].

The US prescribing information provides further information on warnings and precautions related to the use of bimatoprost implant, including regarding risks of corneal adverse reactions (including corneal endothelial cell loss), macular oedema (including cystoid macular oedema), intraocular inflammation, pigmentation changes (e.g. of the iris) and endophthalmitis [9]. Bimatoprost implant should be used with caution in patients with narrow iridocorneal angles or anatomical obstruction that may prohibit settling in the inferior angle. Due to the risk of implant migration into the posterior segment, bimatoprost implant is contraindicated in

patients whose posterior lens capsule is absent or ruptured. Bimatoprost implant is also contraindicated in patients with active or suspected ocular or periocular infections; with corneal endothelial cell dystrophy; and with prior corneal transplantation, or endothelial cell transplants [9].

2.6 Ongoing or Planned Clinical Trials

Five further phase III trials in patients with OAG or OHT are ongoing or planned as part of Allergan's clinical development programme for bimatoprost implant:

- NCT02636946 and NCT02507687 – these randomized, masked, parallel assignment trials are evaluating the IOP-lowering effect and safety of bimatoprost implant compared with selective laser trabeculoplasty in patients who are not adequately managed with topical IOP-lowering medication.
- NCT03850782 – this randomized, masked, parallel assignment trial is evaluating the duration of IOP-lowering effect and safety of as needed administrations of bimatoprost implant in patients who are not adequately managed with topical IOP-lowering medication for reasons other than medication efficacy.
- NCT03891446 – this non-randomized, open-label, parallel assignment extension trial will evaluate the long-term safety and efficacy of bimatoprost implant in patients who completed one of ARTEMIS-1 (NCT02247804), ARTEMIS-2 (NCT02250651), NCT02636946 or NCT02507687 trials and received bimatoprost implant.
- NCT04285580 – this non-randomized, open-label, parallel assignment trial will evaluate the 24-h IOP-lowering effect and safety after a single administration of bimatoprost implant.

3 Current Status

Bimatoprost implant received its first approval on 04 March 2020, in the USA, for use to reduce IOP in patients with open angle glaucoma or ocular hypertension [8, 9].

Compliance with Ethical Standards

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