Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tafluprost

Proprietary Product Name: Saflutan

Sponsor: Merck Sharp & Dohme Pty Ltd

May 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Rejected[1]
Date of decision:	6 May 2011
AAT decision:*	Approved[2]
Date of AAT decision:*	16 December 2011
Active ingredient:	Tafluprost
Product name:	Saflutan
Sponsor's name and address:	Merck Sharp & Dohme (Australia) Pty Ltd Locked Bag 2234, North Ryde NSW 1670
Dose form:	Preservative free eye drops
Strength:	15 micrograms per mL
Container:	Paper coated, aluminium/Polyethylene (PE) foil pouch
Pack size:	Strips of 10s
Approved therapeutic use:	Saflutan is indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension, as monotherapy or as adjunctive therapy to beta blockers.
Dosage:	One drop of Saflutan in the conjunctival sac in the affected eye once daily, to be administered in the evening.
ARTG number:	168803

*AAT= Administrative Appeals Tribunal

[1] The initial Delegate's decision was taken to be confirmed, in accordance with s.60(4) of the *Therapeutic Goods Act 1989* on 27 September 2011. For further details see the *Initial Outcome* section of this AusPAR.
[2] The sponsor appealed to the Administrative Appeals Tribunal for review of the decision not to register Saflutan. The AAT set aside the decision not to register Saflutan and substituted a decision to approve the registration of Saflutan under subsection 25(1) of the *Therapeutic Goods Act 1989*. For further details see the *Final Outcome* section of this AusPAR

Product background

Tafluprost (Saflutan) is a prodrug of a new synthetic prostaglandin F2µ (PGF2µ) analogue in which the isopropyl ester moiety is rapidly hydrolysed to tafluprost acid in plasma and different tissues (for example the cornea). It is claimed that "the chemical modification of PGF2µ to tafluprost acid has resulted in a selective and potent FP receptor agonist with good therapeutic index in the eye".

Drugs of the same class have been considered by Australian Drug Evaluation Committee (ADEC; now called Advisory Committee on Prescription Medicines) previously. Latanoprost, travoprost and bimatoprost have been recommended for approval either as first line or second line glaucoma therapy.

The proposed formulation is a preservative free formulation. The sponsor therefore suggests that it provides "a treatment option to those patients for whom the use of preservative is either not well tolerated or is contraindicated".

Saflutan 15 micrograms/mL eye drops, solution, single dose container is approved in Europe.

Regulatory status

On 15 April 2009, Merck & Co Inc and Santen Pharmaceutical Co Ltd announced a worldwide licensing agreement for tafluprost. In May 2008, unpreserved, single dose (SD) and preserved multidose (MD) formulations were approved in Germany. As of 1 November 2011, the unpreserved formulation of tafluprost has been approved in 45 countries and the preserved formulation of tafluprost has been approved in 19 countries.

Approvals for unpreserved SD tafluprost formulation are shown in Table 1 below.

Table 1. Approvals for unpreserved SD tafluprost formulation (as of 1 November 2011).**

Country	Brand name	Filing date	Approval date
Belgium	Saflutan	9 January 2010	1 February 2011
Canada	Saflutan	16 March 2010	Not yet approved
Denmark	Taflotan	23 April 2007	30 April 2008
France	Saflutan	9 January 2010	28 March 2011
Germany*	Taflotan sine	23 April 2007	7 May 2008
Sweden	Taflotan	23 April 2007	3 July 2008
Switzerland	Saflutan	23 June 2009	28 January 2010
United Kingdom (UK)	Saflutan	23 April 2007	22 October 2009

*Multidose formulation was approved on 7 May 2008.

**Only a sub-set of countries that had approved SD tafluprost as of 1 November, 2011 are shown in Table 1. In total 45 countries had approved SD tafluprost as of 1 November 2011

The approved therapeutic indication in the UK for the preservative free formulation of tafluprost is:

Saflutan is indicated for the reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension. As monotherapy in patients: who would benefit from preservative free eye drops, insufficiently responsive to first line therapy, intolerant or contra-indicated to first line therapy. As adjunctive therapy to beta-blockers.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

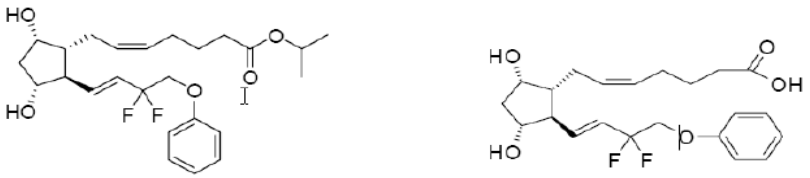
II. Quality findings

According to the PI, the maximum daily dose is one drop per affected eye per day (evening). Therefore assuming a drop size of 50 µL (actual drops have a mean volume of 30-31 µL and less enters the body), the maximum daily dose of tafluprost is 1.5 µg/day.

Drug substance (active ingredient)

Tafluprost is a synthetic analogue of prostaglandin F2α. It is a prodrug of tafluprost acid, which is formed by the hydrolysis of the iso-propyl ester group in tafluprost. Tafluprost acid is a highly potent and selective agonist of the human prostanoid FP receptor (12-fold higher than the related latanoprost).

Figure 1. Chemical structure



Tafluprost Tafluprost acid

tafluprost: CAS# [209860-87-7]

isopropyl (5Z)-7-{1R,2R,3R,5S)-2-[1E)-3,3-difluoro-4-phenoxybut-1-enyl] 3,5-dihydroxycyclopenyl}hept-5-enoate

MW = 452.5 C25H34F2o5

It is manufactured by a multi-step reaction scheme with a final column chromatographic purification step. It has 4 chiral centres, but is presented as a single diastereomer. The drug substance is a liquid and fully dissolved in the finished product and therefore polymorphic form and particle size are not critical. The synthesis leads to the anhydrous, non-solvated material. The specification for tafluprost drug substance includes satisfactory limits for assay (98.0-102.0%). Three of the synthetic impurities and the enantiomer have proposed limits above the International Conference on Harmonisation (ICH) qualification threshold of 0.15%[3]. However given the low dose, these amounts equate to much less than the ICH genotoxic threshold of toxicological concern and they have been accepted on that premise. Unspecified impurities are controlled to the ICH level of NMT 0.10%. The residual solvents were controlled to tighter than ICH guidance.

[3] Note for guidance on impurities testing: Impurities in new drug substances. CPMP/ICH 2737/99.ICH revision of CPMP/ICH/142/95 CPMP/ICH 2737/99. 2002.
<http://www.tga.gov.au/docs/pdf/euguide/ich/273799en.pdf>

Drug product

The product contains the following excipients: polysorbate 80, glycerol, disodium edentate and sodium dihydrogen phosphate. During manufacture the pH is adjusted to 5.6-6.4 with hydrochloric acid or sodium hydroxide. The solution is isotonic. As the product is for single dose use, it is not preserved. It is sterilised by filtration and is filled into single use LDPE ampoules via blow-fill-seal (BFS) process. The ampoules are joined in strips of 10 and each strip is packed into a paper-coated, aluminium/PE foil pouch (to prevent water loss). Microbiology and container safety issues were all resolved.

Specifications for the eye drops ensure British Pharmacopiea/European Pharmacopiea (EP) general requirements for eye drops are met and include requirements for: the potency of active; a limit of NMT 1.0% for tafluprost acid and each unknown degradation product (these limits meet ICH requirements); a limit of NMT 2.5% for total degradation products; pH; osmolality; and sterility (EP).

The shelf life of Saflutan is 36 months when stored at 2-8 ºC. The single-dose strips are to be stored in the laminate pouch to protect the product from evaporation. Once the pouch is opened, the single-dose containers may be stored at room temperature for 28 day period of use within the laminate pouch.

The PI, labels and provisional ARTG record have been finalised with respect to chemistry and quality control. GMP Clearance letters have been issued for two of the sites of manufacture (including the site that manufactures the drug substance).

Bioavailability

This product is for ocular use and is intended to act without systemic absorption. As a consequence no bioavailability data were required to be submitted to the quality evaluator (and none were provided). For this reason the PCES evaluator has not examined the pharmacokinetic section of the draft PI. However, the submission did include pharmacokinetic studies and the PCE evaluated the test method used in these studies to determine tafluprost and tafluprost acid in human plasma samples. This method was acceptable with a limit of quantitation (LOQ) of 10 pg/mL. The Delegate was informed of these facts.

Quality summary and conclusions

Details relating to this submission were presented at the 134th meeting of the Pharmaceutical Subcommittee (PSC). The PSC had no objections to registration provided the issues raised by PCE were resolved to satisfaction of the TGA. The PSC particularly noted two issues:

- The sponsor should provide information on the storage conditions and monitoring of sterile bulk solution in the storage vessel (as storage can occur for 10 days). *This was provided and was acceptable.*
- If the responses to TGA's questions on stability of the finished product and test method used in the pharmacokinetic studies were satisfactory, it could be accepted that the data justify the unopened and open shelf life and the bioanalytical test method used in the Phase III studies are appropriate. *The data was acceptable.*

The PSC also noted the TGA's comments on bioavailability. In this relation it noted that clinical Study 77550 investigated pharmacodynamic endpoints and recommended that the clinical evaluator should consider this study.

Recommendation

Once the outstanding Good Manufacturing Practice (GMP) Clearance letters have been issued, there will be no objections on pharmaceutical chemistry grounds to the registration of the proposed eye drop.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical studies was high. All definitive safety-related studies were conducted under GLP conditions. A comprehensive set of toxicity studies has been undertaken in mice, rats, rabbits, dogs and monkeys. Various routes of administration have been used. There are adequate studies by the clinical route (topical ocular), and the use of other routes (such as intravenous (IV) and subcutaneous (SC)) has allowed higher exposure levels to be attained.

Pharmacology

Primary pharmacology

Tafluprost is a fluorinated analogue of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). It is a pro-drug, undergoing hydrolysis *in vivo* to generate tafluprost acid, which acts as a prostanoid FP receptor agonist. Such agents (for example, bimatoprost, latanoprost and travoprost) are recognised to have a strong ocular hypotensive effect. Although the precise mechanism of action is not known, it is generally believed that they reduce intraocular pressure (IOP) by increasing uveoscleral outflow of aqueous humour.

In vitro studies

Agonist activity for tafluprost and tafluprost acid at the prostanoid FP receptor has been demonstrated *in vitro* in the cat iridial sphincter muscle preparation in published studies. Tafluprost acid was shown to possess sub-nanomolar affinity in radioligand binding experiments with the recombinant human prostanoid FP receptor (expressed in a Human Embryonic Kidney 293 (HEK) cell line; examining inhibition of radioactively labelled (^{3}H)-$PGF_{2\alpha}$ binding). Its potency (K_i, 0.40 nM) was 12-times greater than that of latanoprost acid.

In vivo studies

The ability of tafluprost to reduce IOP was investigated in monkeys. A dose-dependent effect was shown following single topical ocular administration of 0.00002-0.0025% solutions (20 µL) to ocular normotensive animals; tafluprost appeared approximately 10-times more potent that latanoprost. Significant reductions in IOP were observed in ocular hypertensive monkeys with treatment at ≥0.0025% (20 µL; single dose). Upon repeated administration for 5 days (20 µL × 0.0025% or 0.005%) in ocular normotensive monkeys, the effect on IOP became more pronounced with time and persisted for 24 h. Tafluprost increased uveoscleral outflow. A reduction in IOP was seen following intraocular injection of tafluprost acid, but not the other major metabolites.

Secondary pharmacodynamics and safety pharmacology

Screening assays indicated a high degree of specificity for tafluprost acid. The compound did not display affinity for other prostanoid receptors or a suite of non-prostanoid

receptors/ transporters, other than slight affinity for the prostanoid EP_3 receptor (~130-times weaker than for the FP receptor).

Both tafluprost (0.0015% solution) and latanoprost (0.005%) produced a small increase in optic nerve blood flow in the rabbit (topical ocular administration, 50 µL; 2–4 weeks treatment), with a stronger effect produced by tafluprost.

Specialised safety pharmacology studies examined the potential for central nervous system (CNS), cardiovascular and respiratory effects. The effect on uterine smooth muscle was also examined. In mice, marked but transient effects on general activity and behaviour (including ataxic gait, decreased locomotor activity and decreased limb tone) were observed in 1/6 animals after a bolus IV injection of tafluprost at 100 µg/kg (estimated relative exposure based on maximum plasma concentration (C_{max}), >800). No effects on locomotor activity, however, were seen in another study in mice at 100 µg/kg IV. In dogs, tafluprost (as well as $PGF_{2\alpha}$ and latanoprost) increased respiration rate and blood pressure and decreased T wave amplitude following IV administration. Respiratory effects were seen with tafluprost at ≥0.1 µg/kg and cardiovascular effects at ≥1 µg/kg, while the same effects were seen at ≥1 µg/kg and at ≥10 µg/kg with PGF2α and latanoprost. These effects are considered a $PGF_{2\alpha}$ class effect; the greater potency for tafluprost is consistent with the primary pharmacology studies. Relative exposure is estimated to be ~11 at 0.1 µg/kg and 81 at 1 µg/kg (based on C_{max} data obtained on Day 1 in the 39-week IV dog repeat-dose toxicity study).

In isolated dog cardiac Purkinje fibres, tafluprost acid had no significant effect on resting membrane potential, maximum rate of depolarisation, upstroke amplitude or action potential duration at concentrations up to 100 ng/mL. Tafluprost acid (≤100 ng/mL) also did not inhibit the hERG K^+ channel expressed in transfected mammalian cells. This concentration is >3750 times greater than the peak plasma level (total) expected in patients at the maximum recommended human dose. No electrocardiogram (ECG) abnormalities were observed in repeat-dose toxicity studies in monkeys (topical ocular administration; relative exposure based on C_{max}, ≤282), while transient QTc interval[4] prolongation (by 11-17%) using Bazetts correction formula was observed in the 4 week dog study (at 10 µg/kg IV; relative exposure based on C_{max}, ~700). The data indicate that cardiovascular effects are unlikely with clinical use.

Tafluprost acid and $PGF_{2\alpha}$ had effects on the myotonic activity of the isolated rat and rabbit uterus (non-pregnant). Tafluprost acid increased resting tension (at ≥0.1 ng/mL; rat), the frequency of spontaneous contractions (≥1 ng/mL; rat) and maximum tension (≥1 ng/mL; rat and rabbit). This is regarded as a class effect of FP prostanoid receptor agonists; $PGF_{2\alpha}$ in the rat was generally 10 times less potent in comparison. These concentrations of tafluprost acid are approximately 4-40-times the clinical C_{max} (for total drug).

Pharmacodynamic drug interactions

Absorption of ^{3}H-tafluprost-related radioactivity into the eye and the systemic circulation was seen to be very rapid following topical ocular administration of ^{3}H-tafluprost in laboratory animal species (rat and cynomolgus monkey). Following single ocular instillation of ^{3}H-tafluprost to rats and monkeys, peak plasma levels of radioactivity were reached at 5 min post-dose. Conversion to tafluprost acid in the eye was rapid, with tafluprost itself frequently not detected in plasma. Following topical ocular administration of tafluprost in humans, the time to maximal plasma concentration (T_{max}) for tafluprost

[4] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.

acid was 10 min. Plasma levels of tafluprost acid also declined rapidly. Rapid absorption, conversion to tafluprost acid and rapid clearance of tafluprost acid were also observed for the other routes of administration tested in animals (IV and SC). C_{max} and AUC of tafluprost acid were dose-proportional and there was no evidence of sex differences or drug accumulation with repeat dosing in the studies.

^{3}H-Tafluprost-derived radioactivity was rapidly distributed in ocular and systemic tissues following topical ocular administration in the rat and monkey. Levels declined rapidly in most ocular tissues over 24 h but more slowly in the lens. The systemic tissue distribution profile suggests that tafluprost and/or its metabolites pass through the nasolacrimal duct into the oral cavity to be absorbed and distributed to various tissues. Levels of radioactivity in systemic tissues were much lower compared to ocular tissues, with the highest systemic concentrations present in the organs of excretion. In a comparative absorption study in rabbits, between preservative-free and preservative-containing tafluprost ophthalmic solution the presence of benzalkonium chloride (BAK) in the ophthalmic solution did not significantly affect the levels of tafluprost acid measured in the aqueous humour following topical ocular administration of tafluprost. Metabolism of tafluprost to tafluprost acid was catalysed by carboxylesterase in the cornea (shown in the rabbit). Experiments with recombinant human cytochrome P450 enzymes (CYPs) indicated a negligible role in the metabolism of tafluprost acid, and treatment with tafluprost at 100 µg/kg/day IV for 26 weeks did not induce drug metabolizing hepatic enzymes in rats. Further metabolism of tafluprost acid occurred in all species, with the major metabolites common to all species. The drug was excreted as metabolites in both urine and faeces; biliary excretion of metabolites was demonstrated in the rat.

Pharmacokinetics

Absorption of ^{3}H-tafluprost-related radioactivity into the eye and the systemic circulation was seen to be very rapid following topical ocular administration of ^{3}H-tafluprost in laboratory animal species (rat and cynomolgus monkey). Following single ocular instillation of ^{3}H-tafluprost to rats and monkeys, peak plasma levels of radioactivity were reached at 5 min post-dose. Conversion to tafluprost acid in the eye was rapid, with tafluprost itself frequently not detected in plasma. Following topical ocular administration of tafluprost in humans, the time to maximal plasma concentration (T_{max}) for tafluprost acid was 10 min. Plasma levels of tafluprost acid also declined rapidly. Rapid absorption, conversion to tafluprost acid and rapid clearance of tafluprost acid were also observed for the other routes of administration tested in animals (IV and SC). C_{max} and AUC of tafluprost acid were dose-proportional and there was no evidence of sex differences or drug accumulation with repeat dosing in the studies.

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Toxicology

Relative exposure

Exposure ratios in the nonclinical studies have been calculated based on animal: human plasma C_{max} and AUC_{0-t} values for tafluprost acid for consideration of systemic effects, and (for studies by the topical ocular route) as daily dose comparisons for consideration of local effects on the eye (Tables 1 and 2). Relative exposure levels in the studies were usually very high.

Table 1. Relative exposure in repeat-dose toxicity and carcinogenicity studies.

Study	Species	Duration	Route	Dose		C_{max}* (ng/mL)	AUC_{0-t}* (ng·h/mL)	Relative exposure		
				µg/eye /day	µg/kg /day			Systemic		Local[c]
								C_{max}[a]	AUC[b]	
1241/040	**Mouse** (CD-1)	13 weeks	SC	–	3	–	–	24#	30#	–
				–	10	–	–	79#	100#	–
				–	30	6.33	2.17	238	301	–
				–	100	13.7	6.44	515	894	–
1241/047		78 weeks	SC	–	10	1.74	0.604	65	84	–
				–	30	5.04	2.57	189	357	–
				–	100	17.2	9.81	647	1363	–
1241/018	**Rat** (SD)	4 weeks	IV	–	10	26.8	1.70	1008	236	–
				–	30	108.8	6.30	4090	875	–
				–	100	379.4	26.4	14263	3667	–
1241/031		26 weeks	IV	–	10	153.3	9.09	5763	1263	–
				–	30	219.3	14.8	8244	2056	–
				–	100	374.9	51.2	14094	7111	–
1241/039		13 weeks	SC	–	3	–	–	25#	53#	–
				–	10	2.25	1.26	85	175	–

Study	Species	Duration	Route	Dose		C_{max}* (ng/mL)	AUC_{0-t}* (ng·h/mL)	Relative exposure		
				µg/eye /day	µg/kg /day			Systemic		Local[c]
								C_{max}[a]	AUC[b]	
				–	30	7.08	5.97	266	829	–
MP03279		2 years	SC	–	3	0.73	0.451	27	63	–
				–	9	3.15	3.04	118	422	–
				–	30	10.3	11.9	387	1653	–
992506	**Dog** (Beagle)	4 weeks	IV	–	0.1	0.21	–	8	5#	–
				–	1	2.33	0.385	88	53	–
				–	10	18.6	4.12	699	572	–
1241/030		39 weeks	IV	–	0.1	0.17	–	6	4#	–
				–	1	1.44	0.319	54	44	–
				–	10	12.6	3.10	474	431	–
1241/012	**Monkey** (Cyno-molgus)	4 weeks	topical ocular (single eye; twice daily)	0.3	0.067–0.1	–	–	6#	4#	0.7
				3	0.67–1	–	–	56#	43#	7
				30	6.7–10	7.51	1.53	565	425	67
1241/020		13 weeks		0.3	0.075–0.1	–	–	6#	4#	0.7
				3	0.75–1	0.74	–	56	39#	7
				30	7.5–10	5.81	1.39	437	386	67
1241/034		52 weeks		0.3	0.075–0.1	–	–	4#	3.4#	0.7
				3	0.75–1	0.54	–	41	34#	7
				30	7.5–10	4.38	1.23	329	342	67
77551	**Human** [MRHD, 900 ng]		topical ocular	0.45	0.018	0.0266	0.0072	–	–	–

* = of tafluprost acid (active metabolite); [a] = calculated as animal:human C_{max} multiplied by dosing frequency;
[b] = calculated as animal:human AUC0–t multiplied by dosing frequency;
[c] = calculated as animal:human ocular dose/day; – = not detected/not calculated/not applicable;
# = estimate based on linear extrapolation; once daily administration for SC and IV routes;

Note that exposure ratios in the monkey studies refer to a 24 h period, ratios after each dose are half the given value; MRHD = maximum recommended human dose (based on once daily bilateral use with 30 µL drop volume);
Human body weight of 50 kg assumed.

Table 2. Relative exposure in reproductive toxicity studies

Study	Species	Type	Route	Dose (µg/kg/day)	C_{max}* (ng/mL)	AUC_{0-t}* (ng·h/mL)	Relative exposure[a]	
							C_{max}	AUC
1241/32	**Rat** (SD)	fertility	IV	10	26.8¶	1.70¶	1008	236
				30	108.8¶	6.30¶	4090	875
				100	379.4¶	26.4¶	14263	3667
1241/29		embryofetal development	IV	3	9.13	–	343	227#
				10	62.4	5.45	2346	757
				30	136.9	5.59	5147	776
MP04098		pre-/postnatal development	IV	0.3	–	–	34#	23#
				1	–	–	114#	76#
				3	9.13†	–	343	227#
				10	62.4†	5.45†	2346	757
1241/28	**Rabbit** (NZW)	embryofetal development	IV	0.03	–	–	3#	–
				0.1	0.26	–	10	–
				0.3	1.18	–	44	–
1241/35			IV	0.001	<0.02	–	<0.75	–
				0.003				
				0.01				
77551	**Human** [MRHD, 900 ng]		topical ocular	0.018	0.0266	0.0072	–	–

* = of tafluprost acid (active metabolite); – = not detected/not calculated/not applicable;
a = calculated as animal:human Cmax or AUC0–t; ¶ = based on data in the 4-week IV rat study (1241/018);
† = based on data from the embryofetal development study (1241/29); # = estimate based on linear extrapolation;
Reported pharmacokinetic parameters are for GD17 (rat) or GD19 (rabbit);
MRHD = maximum recommended human dose (based on once daily bilateral use; 30 µL drop).

Acute toxicity

In single-dose toxicity studies, neither oral (PO) administration of tafluprost at dose levels up to 100 mg/kg nor IV administration at up to 3 mg/kg produced significant signs of toxicity in rats. In dogs, single IV administration at ≥3 µg/kg produced salivation, vomiting, moderate miosis, irregular respiration and increased heart rate. At 30 µg/kg, the miosis was severe and blood pressure was also increased. No adverse effects were noted at 0.3 µg/kg IV, associated with a C_{max} for tafluprost acid estimated to be ~24 times the level in humans at the maximum recommended clinical dose.

Repeat-dose toxicity

Studies of up to 13 weeks duration were conducted in mice, 26 weeks in rats, 39 weeks in dogs and 52 weeks in cynomolgus monkeys. Studies in rodents and dogs used SC and/or IV administration, while the studies in monkeys used the clinical route (topical ocular). Dosing in monkeys was to one eye (allowing the contralateral eye to serve as a further control), involved more frequent administration than is proposed clinically (twice compared to once daily) and used strengths of tafluprost more than 33-times higher than in the intended marketed dose of Saflutan. The excipient profile of the ophthalmic solutions tested differed from the proposed product in that they contained the preservative benzalkonium chloride (absent in Saflutan) and different concentrations (higher or lower) of polysorbate 80. The duration of the pivotal studies, the species used, group sizes and the use of both sexes were consistent with the relevant European Union (EU) guideline (CPMP/SWP/1042/99[5]).

Systemic effects

Observed systemic effects comprised changes in haematological parameters and bone, spleen, liver and kidney histology in rats and clinical signs in dogs. No systemic toxicity was evident in mice (≤100 µg/kg/day SC for 3 months; relative exposure based on C_{max}, >500) or monkeys (≤30 µg/day by topical ocular administration for up to 12 months; relative exposure, ~330).

In rats, slight reductions in red blood cell indices were observed in males treated intravenously with 100 µg/kg/day for 4 weeks; these were reversible and not accompanied by histopathological changes. Similar haematological changes were observed in both sexes in the 6-month study (mostly at 30 and 100 µg/kg/day IV), as well as hyperostosis and myelofibrosis in the femur and/or sternum (both sexes) and increased haemopoiesis in the marrow of the femur (males only) at all dose levels (≥10 µg/kg/day; relative exposure based on C_{max}, >5700). Haemopoiesis was increased in the spleen and evident in the liver. A No Observed Effect Level (NOEL) was established. Increased haemopoiesis was also observed in the spleen of male rats treated at 30 µg/kg/day SC for 13 weeks (relative exposure based on C_{max}, ~265) without changes in haematology. These effects are likely to be related to the pharmacological effects of tafluprost, since prostaglandins can stimulate osteoblast recruitment and activity, leading to new bone formation and a reduction in the bone marrow cavity. Prostaglandins also influence haemopoiesis directly. Corticomedullary mineralisation in the kidney (a common spontaneous finding) was increased in incidence and severity in female rats treated at ≥10 µg/kg/day IV for 26 weeks and at 30 µg/kg/day SC for 13 weeks. This may be related to effects on calcium/phosphorus balance, occurring secondary to effects on bone.

Transient clinical signs (emesis/retching, salivation and increase heart rate) were associated with IV dosing in dogs. These were occasional at 1 µg/kg/day (relative exposure based on C_{max}, 54) and frequent at 10 µg/kg/day (relative exposure, 474). Slight

[5] Note for guidance on repeated dose toxicity.
<http://www.tga.gov.au/docs/pdf/euguide/swp/104299en.pdf>

to moderate and moderate to severe miosis was also observed at these respective dose levels. An increase in urine volume was observed in the 4-week but not the 9-month study. These findings in dogs are considered to be related to the pharmacological activity of the prostaglandins and were absent at 0.1 µg/kg/day (relative exposure, 6). The bone and haematological changes identified in rats were not observed in dogs (≤10 µg/kg/day IV for 9 months; relative exposure, ≤474).

Ocular effects

Treatment with tafluprost by topical ocular administration in monkeys at up to 67 times the clinical dose produced local effects only. In addition to the desired pharmacological effect (reduction in IOP), treatment caused a change in iris colour (darkening), slight sinking of the upper eyelid, and discolouration (blue-grey) of the lower eyelid. Effects on the iris were observed at all doses (≥0.3 µg/day; a third lower than the clinical dose), and on the eyelids mostly at ≥3 µg/day (~7 times the clinical dose). Microscopic examination revealed that the changes in iris and eyelid colour were associated with increased pigment; there was no evidence of melanocyte proliferation. The effects became more evident as treatment continued. Changes in iris colour in animals treated for 13 weeks were not reversed following a 4-week treatment-free period. The findings are recognised to be class effects of the prostaglandin $F_{2\alpha}$ analogues, and while not considered toxic in nature may be considered cosmetically undesirable. Focal inflammation in the eyelid epithelium was also seen, but this was minimal in severity and only occurred at 30 µg/day (67 times the human dose; absent at 7 times the human dose).

Studies examining ocular irritation were conducted in rabbits and monkeys. Animals were given 10 topical ocular doses at 30 min intervals. Strengths of 0.005–0.5% tafluprost were tested in rabbits and 0.0005–0.05% in monkeys. There was no evidence of significant ocular irritation in rabbits; effects observed (an increase in blinking frequency and very slight to slight conjunctival redness, which resolved by Day 2) were similar in the vehicle and tafluprost-treatment groups (>300 times the clinical strength of the active ingredient). In monkeys there was some evidence of increased ocular irritation compared to vehicle at the 0.005% and 0.05% dose levels. A slight increase in conjunctival hyperaemia compared to controls and positive corneal fluorescein staining were observed from the 0.005% dose level (>3-times the clinical strength) together with slight corneal opacity and chemosis of the palpebral conjunctiva at 0.05% (33-times the clinical strength). Unlike the proposed product, the solutions tested contained benzalkonium chloride as a preservative. This excipient is known to have irritant properties. It can therefore be expected that the formulation proposed for registration will be better tolerated locally in comparison.

Genotoxicity and carcinogenicity

The potential genotoxicity of tafluprost was examined in the standard battery of tests with negative results returned in assays for bacterial gene mutation and for chromosomal aberrations *in vitro* (Chinese hamster lung cells) and *in vivo* (micronucleus test in mouse bone marrow). The studies were conducted in line with the relevant guidelines[6].

The carcinogenic potential of tafluprost was investigated in an 18-month study in mice and a 2-year study in rats. Administration was by the SC route which is considered appropriate. Group sizes were appropriate and dual control groups were used, as recommended in the relevant EU Guideline (CPMP/SWP/2877/00[7]). Suitable dose levels were selected, with the highest dose levels producing very high multiples of the anticipated clinical exposure and usually suppression of body weight gain. There was no

[6] Relevant guidelines are published at
<http://www.tga.gov.au/docs/html/euguide/euad_nonc.htm#nonclinicaltoxicology>
[7] Note for Guidance on Carcinogenic Potential.
<http://www.tga.gov.au/docs/pdf/euguide/swp/287700en.pdf>

evidence of a treatment-related increase in tumour incidence in either mice (≤100 µg/kg/day; relative exposure, ~650 based on C_{max} and >1360 based on AUC) or rats (≤30 µg/kg/day; relative exposure, ~390 based on C_{max} and ~1650 based on AUC).

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility and early embryonic development, embryofetal development and pre- and postnatal development). All studies used the IV route, which is appropriate based on pharmacokinetic considerations. The number of animals/group and the timing and duration of treatment were considered to be appropriately chosen.

Placental transfer of radioactivity was observed in rats following a topical ocular dose of ^{3}H-tafluprost, with fetal exposure (based on area under the concentration versus time curve (AUC)) two-thirds that of the maternal exposure. Excretion of ^{3}H-tafluprost-derived radioactivity in milk was shown in rats following topical ocular administration. The maximum likely dose a pup would obtain from the consumption of maternal milk was calculated to be ~0.1% of the maternal dose.

Male and female fertility, mating performance and early embryonic development were unaffected in rats at doses up to 100 µg/kg/day (relative exposure, >14000 based on C_{max} and >3600 based on AUC). In embryofetal development studies in rats, post-implantation loss was increased at ≥30 µg/kg/day, fetal weight was decreased at >10 µg/kg/day; skull and spinal malformations and increased vertebral skeletal variations were observed in fetuses at ≥10 µg/kg/day. The NOEL for embryofetal development in the rat is 3 µg/kg/day (relative exposure, ~340 based on C_{max} and 230 based on AUC). Rabbits were significantly more sensitive to the reproductive toxicity of tafluprost than rats; post-implantation loss was increased at ≥0.03 µg/kg/day and total loss was reported at ≥0.3 µg/kg/day. Treatment at 0.03 µg/kg/day produced malformations of the skull, brain and spine (cranioschisis, exencephaly, spina bifida, absent medulla oblongata and thalamus; estimated relative exposure based on C_{max}, 3)[8]. The NOEL for embryofetal development in the rabbit is considered to be 0.01 µg/kg/day; tafluprost acid was not detectable in plasma at this dose (<20 pg/mL) and exposure is below that of humans at the maximum recommended clinical dose (relative exposure, <0.75).

In the pre- and postnatal development study in rats, poor nursing behaviour was seen in a small number of dams at each dose level (0.3–10 µg/kg/day) and this resulted in the death of offspring within 2 days at ≥1 µg/kg/day. A large increase in stillbirths and/or deaths of pups immediately after birth was observed at all doses (estimated relative exposure, 34–2350 based on C_{max} and 23–760 based on AUC [using data from the embryofetal development study]), but in particular at the high-dose level. No treatment-related effects on parturition were noted. Pup birth weight and survival to Day 4 were significantly reduced and pinna unfolding delayed at 10 µg/kg/day (estimated relative exposure, ~2350 based on C_{max} and 760 based on AUC). Pup reproductive function and other developmental parameters were unaffected. No NOEL for perinatal effects was established (<0.3 µg/kg/day); the NOEL for postnatal development is 0.3 µg/kg/day (relative exposure, 34 based on C_{max} and 23 based on AUC).[9]

[8] The sponsor commented that they do not consider the absent medulla oblongata or thalamus in rabbits to be test article related since it was observed in isolation in only 1 fetus.
[9] The sponsor commented that in the pre- and postnatal rat study, they consider the NOEL for perinatal effects (including stillbirths and deaths of pups immediately after birth) to be 0.3 µg/kg/day (relative exposure, 34 based on C_{max} and 23 based on AUC).

Pregnancy categorisation

The sponsor has proposed Pregnancy Category B3. Based on findings of embryofetal lethality and teratogenicity in both laboratory animal species, the absence of a margin of exposure at the NOEL for malformations in the rabbit and the absence of a NOEL for increased perinatal mortality in rat pups, placement in category B3 is not considered appropriate. The product should instead be assigned Pregnancy Category D. This category is for "drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage[10]".

Use in children

Saflutan is not proposed for paediatric use. No specific studies were conducted in juvenile animals.

Skin sensitisation

There was no evidence of skin sensitisation from ophthalmic solutions containing tafluprost at 0.005% or 0.05% in a standard assay in guinea pigs.

Immunotoxicity

There was no indication of immunotoxicity in the repeat-dose toxicity studies. In line with this, and given there is no postulated mechanism for an immunological risk from tafluprost, no specific studies were conducted in accordance with ICH Guideline S8[11].

Metabolites / impurities

No specific studies were conducted. Tafluprost acid, the active species formed by hydrolysis, was routinely monitored in the tafluprost toxicity studies.

Nonclinical summary and conclusions

- The sponsor has conducted adequate studies on the pharmacodynamics, pharmacokinetics and toxicity of tafluprost, with all definitive safety-related studies conducted in compliance with Good Laboratory Practice (GLP) regulations and in accordance with relevant guidelines.
- Tafluprost acid was shown to have sub-nanomolar affinity for the recombinant human prostanoid FP receptor *in vitro*, with potency 12-times greater than that of latanoprost acid. Topical ocular administration of tafluprost significantly reduced IOP in ocular normotensive and hypertensive monkeys in a dose-dependent manner. The effect was long lasting (persisting for 24 h) and associated with increased uveoscleral outflow of aqueous humour.
- Secondary pharmacodynamic studies indicated a high degree of receptor specificity for tafluprost acid. Tafluprost (and latanoprost) produced a small increase in optic nerve blood flow in the rabbit. Safety pharmacology studies covered the CNS, cardiovascular and respiratory systems, as well as examining effects on uterine smooth muscle. There were no consistent effects on general activity, behaviour or

[10] The sponsor did not agree with the above wording for Pregnancy Categorisation. The sponsor had submitted a response to the TGA explaining why Pregnancy Category D is not the appropriate category for tafluprost and that Pregnancy Category B3 is the appropriate category. The TGA feedback was pending.
[11] EMEA/CHMP/167235/2004. Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals. <http://www.tga.gov.au/docs/pdf/euguide/emea/16723504en.pdf>

locomotion in mice at ≤100 µg/kg IV (estimated relative exposure, >800). Tafluprost increased respiration rate and blood pressure and decreased T wave amplitude in the dog at ≥0.1 or ≥1 µg/kg (relative exposure, ~11–80); these effects were also seen with $PGF_{2\alpha}$ and latanoprost. No inhibition of the hERG K^+ channel by tafluprost acid was evident *in vitro* at a concentration >3750-times the clinical C_{max}; action potential parameters in isolated dog Purkinje fibres were also not significantly affected. No ECG abnormalities were observed in tafluprost-treated monkeys (relative exposure, ≤282), while transient QTc interval prolongation was observed in dogs, but at a very high exposure margin only (~700). Effects on the contractile activity of the isolated rat and rabbit uterus (increases in resting tension, frequency of spontaneous contractions and maximum tension) were seen with tafluprost (as well as $PGF_{2\alpha}$).

- Pharmacokinetic studies indicated very rapid systemic absorption of tafluprost acid following topical ocular administration of tafluprost in laboratory animal species and humans. Conversion of tafluprost to tafluprost acid in the eye was rapid, with the unchanged drug frequently not detected in plasma after dosing. Exposure of tafluprost acid was dose-proportional and there was no evidence of sex differences or drug accumulation with repeat dosing. Systemic distribution of ^{3}H-tafluprost related radioactivity was rapid and wide but the levels were low. Metabolism of tafluprost to tafluprost acid was shown to be mediated by carboxylesterase in the cornea in the rabbit. Further metabolism of tafluprost acid generated major metabolites that were common to the nonclinical species and humans; this metabolism did not involve CYPs to any significant extent. Excretion was rapid, in the form of metabolites and via urine and bile/faeces.
- Tafluprost was well tolerated in single-dose toxicity studies in rats at ≤100 mg/kg PO or 3 mg/kg IV, and in dogs at 0.3 µg/kg IV. Higher doses in dogs (3–30 µg/kg IV) produced clinical signs and cardiovascular and respiratory effects.
- Pivotal repeat-dose toxicity studies were conducted in rats (6 months duration; IV administration), dogs (9 months; IV) and cynomolgus monkeys (12 months; topical ocular administration). Major findings in rats were limited to effects on bone (hyperostosis), bone marrow/haemopoiesis and red blood cell indices (slight reductions) at large margins of exposure. These effects are considered likely to be pharmacologically mediated. Transient clinical signs (emesis/retching, salivation, increased heart rate and miosis) - but not bone and haematological changes - were observed in dogs following IV dosing. No systemic toxicity was observed in monkeys treated with tafluprost by the topical ocular route (relative exposure, ≤330).
- Ocular effects were seen in monkeys and comprised changes in iris colour (darkening), slight sinking of the upper eyelid and discolouration (blue-grey) of the lower eyelid. Effects on the iris occurred at subclinical dose levels (relative exposure, ≥0.7) and on the eyelid mostly at ≥7-times the clinical dose. The changes in iris and eyelid colour were associated with increased pigment; the iris colour changes were not seen to be reversed after a 4-week treatment-free period. Ocular irritation studies in rabbits and monkeys indicated only slight effects with solutions of tafluprost.
- There was no evidence of genotoxicity in adequately conducted in vitro and in vivo studies. Tafluprost was not carcinogenic in an 18-month study in mice or in a 2-year study in rats, involving administration by the SC route and very high multiples of the clinical exposure level.
- Placental transfer of tafluprost and/or its metabolites and excretion in milk were demonstrated in the rat following topical ocular administration. Tafluprost did not affect male and female fertility in rats (≤100 µg/kg/day IV). In embryofetal development studies, the drug (administered IV) caused increased post-implantation loss and was teratogenic in both species tested (rats and rabbits), with malformations

of the skull, spine and/or brain noted. In the rat, fetal vertebral skeletal variations were also increased and fetal weight was decreased. A high multiple of the clinical exposure is evident at the NOEL for effects on embryofetal development in the rat (3 µg/kg/day; ~340-times the clinical C_{max}) but not the rabbit, where exposure at the NOEL (0.01 µg/kg/day) was subclinical (<0.75-times the clinical C_{max}). Poor nursing behaviour was seen in the rat pre-/postnatal development study, as well as increased stillbirths and deaths of pups immediately after birth, decreased birth weight and some evidence of delayed development. No NOEL for perinatal effects could be established while the NOEL for effects on postnatal development was 0.3 µg/kg/day (relative exposure, 34).

- There was no evidence of skin sensitisation in guinea pigs, or evidence of immunotoxicity in the repeat-dose toxicity studies.

Conclusions and recommendation

- The nonclinical current Australian submission contained no major deficiencies.
- Primary pharmacology studies, showing prostanoid FP receptor agonist activity and high potency in vitro, and reductions in intraocular pressure *in vivo*, support the drug's use for the proposed indications.
- Safety pharmacology studies indicate no likely effects on the CNS, cardiovascular and respiratory systems with clinical use.
- Treatment related effects seen in the repeat-dose toxicity studies were likely all related to the pharmacological activity of tafluprost. Systemic effects, when seen, were unique to particular species and evident only at exposure levels well above the clinical exposure. Changes in iris colour and effects on the eyelids are recognised to be class effects of the $PGF_{2\alpha}$ analogues. The studies in monkeys indicate a modest exposure margin for effects on the eyelid and no margin in relation to effects on iris colour. While these local effects are not toxicologically significant, they are undesirable. Such changes were also apparently observed in the clinical trials, and their significance is better addressed based on the clinical data set.
- The drug is not considered to pose a genotoxic or carcinogenic hazard.
- Reproductive toxicity studies, showing embryofetal lethality, teratogenicity and other effects, raise concerns with regard to use in pregnancy. The rabbit was considerably more sensitive to tafluprost compared to the rat, consistent with the species' known high sensitivity to prostaglandins. Given the data, Pregnancy Category D (rather than B3 as proposed by the sponsor) is considered appropriate.[10] There are no nonclinical objections to the registration of Saflutan for the proposed indications.

IV. Clinical findings

Introduction

Tafluprost is formulated in aqueous solution for topical use on the eye. Two different formulations of the ophthalmic solution have been developed. The first contains the preservative benzalkonium chloride (BAK) in addition to the listed ingredients and is packed in multi-dose containers. The second formulation is preservative free and is packed in single dose containers. The clinical data submitted with the current Australian submission are identical for both formulations. The sponsor is only seeking registration in Australia for the preservative free formulation.

At the time of this submission, no studies with tafluprost have been conducted in paediatric patients. Glaucoma occurs rarely in children and surgical intervention is the mainstay of treatment. The sponsor stated that with low prevalence of medically treated disease and the need to conduct lengthy safety follow up, a paediatric development program may not be feasible. It has stated that an assessment of this feasibility is currently being conducted.

A risk management plan (RMP) Version 3 dated 30 April 2009 for the European Union has been provided. It is unclear if this is to cover Australia as well. [12] The sponsor certifies that all clinical studies were conducted in accordance with Good Clinical Practice guidelines with appropriate permission from independent ethics committees or institutional review boards and health authorities.

Pharmacokinetics

The pharmacokinetics of tafluprost were examined in six clinical studies involving 128 healthy adult subjects (fifty of these subjects were Japanese). Unfortunately, four of these studies used a bioanalytical method with insufficient sensitivity to determine the PK of tafluprost or its active metabolite, tafluprost acid; however, two studies used an analytical method with improved sensitivity for tafluprost acid that allowed PK analysis of tafluprost acid.

Methods

Bioanalytical methods for human studies

The two liquid chromatography–mass spectrometry (LC-MS/MS) based assay methods used to quantify the levels of tafluprost (AFP-168) and tafluprost acid (AFP-172) in plasma and the aqueous humour were validated in the nonclinical data. The former study used gradient reverse-Phase LC-MS/MS and the lower limit of quantification of the method was 0.2 ng/mL for AFP-168 and 0.1 ng/mL for AFP-172. At these concentrations, the required precision and accuracy criteria (≤ 20%) were met. This method was used in two studies (P74450, P74453); however, the sensitivity of this method was not sufficient for analysis of plasma samples, although the equivocal results may have resulted from the long period (> 21 months) of sample storage. Therefore a new method with improved sensitivity was developed for tafluprost acid (the active form of the drug) and this method was used for clinical trials P15005 and P77551.

Pharmacokinetic data analysis

A repeated measures analysis of variance was used for the evaluation of the tafluprost acid plasma concentrations, a nonparametric analysis of variance model for $AUC_{0\text{-last}}$ (the area under the plasma concentration time curve from time zero to the last measurable time point) and C_{max}, and descriptive statistics were reported for T_{max}. Paired t-tests were used to compare differences between individual time points or treatments. To compare 0.0025%, 0.005% tafluprost and placebo individual t-tests were performed at each time point.

Absorption

Bioavailability

Following topical ocular application, the bioavailability of tafluprost in the eye was studied in monkeys [PK014, PK016]. Following topical administration of 1 µg ^{3}H-tafluprost to the monkey eye, the T_{max} and C_{max} of radioactivity in the aqueous humour were 2 hours and

[12] The sponsor later confirmed that this document covers Australia as well.

approximately 21-30 ngEq/mL, respectively. By 24 hours, the concentration had declined to about 0.3-0.4 ngEq/mL. Several studies have attempted to define the systemic bioavailability of tafluprost. However, in four combined pharmacodynamic and pharmacokinetic Phase I clinical trials (see below), neither tafluprost nor tafluprost acid were quantifiable in plasma due to the low concentrations, the low sensitivity of assay methods. and possibly due to the fact that the examination of samples was delayed beyond the shown stability of 21 months. In Study 77551, the Day1 C_{max} and $AUC_{0\text{-}last}$ of tafluprost acid for the preserved solution was 24.4 pg/mL and 405.9 pg.min/mL, respectively, and at Day 8 it was 31.4 pg/mL and 581.1 pg.min/mL, respectively.

Bioequivalence

Study **77551** examined the pharmacokinetics and safety of two formulations of tafluprost (preserved and unpreserved) 0.0015% ophthalmic solution. The plasma concentrations of tafluprost acid for the two formulations were low at all time points following single (Day 1) and repeated (Day 8) topical administrations of 0.0015% preserved and unpreserved tafluprost eye drops. For the preservative containing formulation, the mean C_{max} and $AUC_{0\text{-}last}$ values were lower on Day 1 (24.4 pg/mL and 405.9 pg*min/mL, respectively), than on Day 8 (31.4 pg/mL and 581.1 pg*min/mL, respectively). By contrast, the mean C_{max} values (26.2 and 26.6 pg/mL, Day 1 and 8, respectively) and $AUC_{0\text{-}last}$ values (394.3 and 431.9 pg*min/mL, Day 1 and 8, respectively) for the unpreserved formulation were similar on both Days 1 and 8. In spite of these differences, no statistically significant differences were identified between the PK parameters for the unpreserved and preserved formulations and no statistically significant differences were detected between Day 1 and Day 8 for either formulation. However, it must be pointed out that the data, in particular the $AUC_{0\text{-}last}$ values, were characterised by high standard deviations (SDs). The pre-dose concentrations of tafluprost acid were below the lower limit of quantification (10 pg/mL) for both formulations on both days. Mean concentrations of AFP-172 peaked at 10 minutes and cleared rapidly from the circulation on both days, so that it could not be quantified in any subject beyond one hour after dosing.

Influence of food

No studies examined the effect of food on the pharmacokinetics of tafluprost.

Distribution

The binding of tafluprost acid to human serum albumin was investigated using ultra-filtration and LC-MS/MS. At a concentration of 500 ng/mL (~10-6M), the binding was 99% [PK017]. Thus marked binding of tafluprost acid to albumin can be expected to occur in plasma.

Elimination

No studies examining the excretion of tafluprost in humans were provided.

Metabolism

A number of *in vitro* studies have examined the metabolism of tafluprost in human hepatocytes [PK022, PK023, and PK028]. These studies have identified that the isopropyl ester moiety of tafluprost undergoes rapid hydrolysis to form the active and potent metabolite tafluprost acid. In addition, the 1,2-dinor- and 1,2,3,4-tetranor-tafluprost acid metabolites as well as glucuronide conjugated metabolites were detected. Phenyl ring hydroxylated metabolites of both beta-oxidation products were also demonstrated. Generally the metabolism of tafluprost by human hepatocytes was rapid and extensive. No metabolism of tafluprost acid by human recombinant CYP450 occurred.

Pharmacokinetics of metabolites

Tafluprost is a prostaglandin pro-drug that is rapidly hydrolysed to form tafluprost acid. In four studies in which the plasma levels of tafluprost were examined, no tafluprost could be detected. Given these findings, the investigators contention that the main pharmacological activity resides in this metabolite is most likely true. However, the samples in these same four studies were kept beyond the known stability (21 months) of the drug and therefore the lack of detection of tafluprost may have resulted from its breakdown rather than the low levels detected.

Consequences of possible genetic polymorphism

In vitro studies did not identify metabolism of tafluprost acid by human recombinant CYP450, therefore, it is unlikely that genetic polymorphism would affect its metabolism.

Dose proportionality and time dependency

The pharmacokinetics of four concentrations of tafluprost (AFP-168) eye drops (0.0001%, 0.0005%, 0.0025% and 0.005%) after single and twice daily doses were examined in study **WW-74450-EU**. However, due to the fact that the analysis of the samples was delayed beyond the known stability of 21 months, the pharmacokinetic results should be regarded as suggestive only. All analyses of the plasma concentrations were below the limit for quantification except for 3 samples.

The pharmacokinetics of two concentrations of tafluprost eye drops (0.0025% and 0.005%), given once daily for 7 days were examined in study **WW-74452-EU**. However, all analyses of the plasma concentrations of tafluprost and tafluprost acid were below the limit of quantification except for a few pharmacokinetic outliers.

Pharmacokinetics of preservative containing tafluprost (0.0015%) ophthalmic solution were examined in Study 15-005. The plasma concentration profile of tafluprost acid was increased between on Day 1 (after the first dose) and Day 8 (following the eighth dose). Although T_{max} occurred at 10 min after administration of the drug on both days, the mean C_{max} value was 18.4±9.2 pg/mL and 25.2±11.9 pg/mL on Day 1 and Day 8, respectively, (equivalent to a 1.4-fold increase). The corresponding $AUC_{0\text{-last}}$ values were 188.3 ± 128.1 pg.min/mL and 340.2 ± 242.4 pg.min/mL on Day 1 and Day 8, respectively, (1.8-fold increase). The differences in plasma exposure were statistically significant. Tafluprost acid was rapidly eliminated from the circulation, and after 30 min the concentrations were below the limit of quantification.

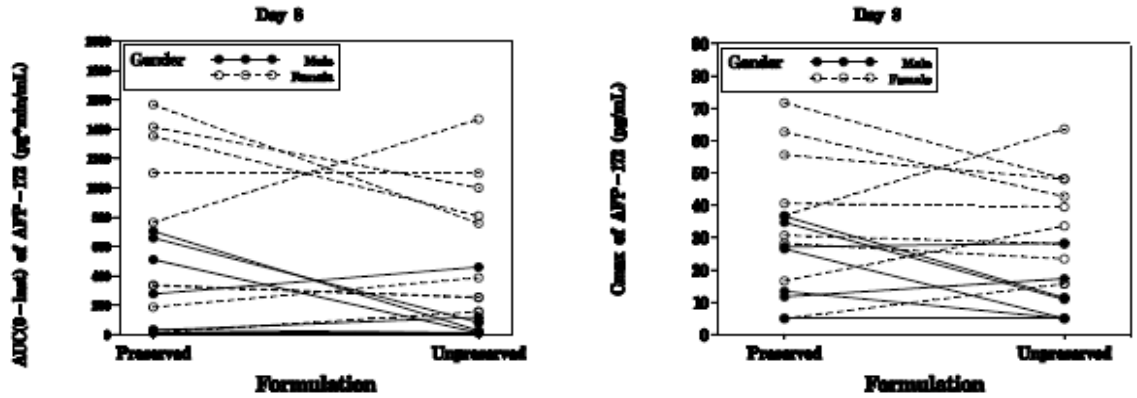
Time dependency

No studies examined the effect of time of dosing on the pharmacokinetics of tafluprost. However, dosing was done at 8pm in almost all tafluprost studies. However, in Study 77551 doses were administered at 8pm and in Study 15005 doses were administered at 8am. Although the derived T_{max} was the same for both studies (10 minutes), $AUC_{0\text{-last}}$ (for example, on Day 1 the morning (am) exposure was lower (188 pg.min/mL) compared to the evening exposure (pm; 406 pg.min/mL) and C_{max} (Day 1, the exposure was 18 versus 24 pg/mL in the am and pm, respectively), were both increased on Days 1 and 8 in Study 77551, which may suggest that a time effect does exist in regard to dosing.

Intra- and inter-subject variability

In Study **77551**, the intra-subject variation was large for both C_{max} and AUC and some female subjects had higher systemic bioavailability (Figure 2). For instance, for the unpreserved formulation on Day 8, the mean and standard deviation for $AUC_{0\text{-last}}$ was 431.9 ± 457.8 pg.min/mL.

Figure 2. Study 77551. Individual Cmax and AUC0-last values of AFP-172 by formulation on Day 8.



Pharmacokinetics in the target population

No studies examined the pharmacokinetics of tafluprost in the target population of patients with glaucoma.

Special populations

The pharmacokinetics of four concentrations of tafluprost eye drops (0.0001%, 0.0005%, and 0.0025% and 0.005%) after single and twice daily doses was examined in healthy Japanese subjects in Study **WW-74451-EU**. Similar to the previous study, all analyses of the plasma concentrations were below the limit for quantification except for one sample.

The pharmacokinetics of tafluprost (0.0025% and 0.005%) eye drops after dosing for one week in healthy Japanese male volunteers was examined in Study **WW-74453-EU**. Once again, all analyses of the plasma concentrations of tafluprost and tafluprost acid were below the limit of quantitation except for one sample.

Evaluators comments on pharmacokinetics in special populations

No meaningful studies have examined the pharmacokinetics of tafluprost in special populations. Therefore, any pharmacokinetic differences that occur between normal, healthy adult and paediatric subjects, patients with renal or hepatic impairment, the elderly or male and female patients are unknown.

Exposure relevant to safety

Study WW-74451-EU, which examined four concentrations (0.0001%, 0.0005%, 0.0025% and 0.005%) and Study WW-74450-EU, which examined three concentrations (0.0001%, 0.0005%, 0.0025%) of tafluprost eye drops both identified dose related ocular (conjunctival) hyperaemia as the most common side-effect. In addition, two studies (WW-74453-EU and WW-74451-EU) identified that tafluprost caused more ocular hyperaemia and photophobia than Xalatan® (Latanoprost). In contrast, Xalatan® caused more blurred vision.

Evaluators overall conclusions

Bioavailability

The T_{max} and C_{max} of radioactivity in the aqueous humour following topical administration of 1 µg radioactively labelled [^{3}H]-tafluprost to the monkey eye were 2 hours and approximately 21-30 ngEq/mL. By 24 hours, the concentration had declined to about 0.3-

0.4 ngEq/mL. These results were in good agreement with a previous study performed in monkeys with latanoprost[13]. Although ^{3}H-tafluprost was not examined in human eye, the penetration of latanoprost into the human eye has been studied and was found to correspond well with that in monkeys[14]. In four studies which attempted to define the systemic bioavailability of tafluprost, neither tafluprost nor tafluprost acid were quantifiable in plasma due to the low concentrations, sensitivity of assay methods and possibly due to the fact that the examination of samples was delayed beyond the shown stability of 21 months.

The plasma concentration profile of tafluprost acid generally increased from Day 1 (after the first dose) to Day 8 following 8 days treatment with 0.0015% tafluprost. For instance, the C_{max} on Day 1 was significantly lower than on Day 8 (18.4 pg/mL and 25.2 pg/mL, respectively, as was the $AUC_{0\text{-last}}$ (188.3 ± 128.1 pg.min/mL, 340.2 ± 242.4 pg.min/mL, respectively). By contrast, the C_{max} occurred after 10 min following administration on both Days 1 and 8.

Biocomparison of formulations

For the preserved and unpreserved formulations of tafluprost 0.0015% ophthalmic solution, the plasma concentrations of tafluprost acid were low at all time points following single and repeated (8 day) topical administrations. For the preservative containing formulation, the mean C_{max} and $AUC_{0\text{-last}}$ values on Days 1 and 8 were 24.4 pg/mL and 405.9 pg*min/mL, respectively, and 31.4 pg/mL and 581.1 pg*min/mL, respectively. For the unpreserved formulation, the mean C_{max} values (26.2 and 26.6 pg/mL, Day 1 and 8, respectively) and $AUC_{0\text{-last}}$ values (394.3 and 431.9 pg*min/mL, Day 1 and 8, respectively) were similar on both days. Although there was a trend toward increase in plasma concentrations from Day 1 to Day 8 for both formulations, no statistically significant differences were identified between the PK parameters for the unpreserved and preserved formulations and no statistically significant differences were detected between Day 1 and Day 8 for either formulation This may have resulted from the high degree of intersubject variability as the data, in particular the $AUC_{0\text{-last}}$ values, were characterised by high SDs. The pre-dose concentrations of tafluprost acid were below the lower limit of quantification (10 pg/mL) for both formulations on both days. Mean concentrations of AFP-172 peaked at 10 minutes and cleared rapidly from the circulation on both days and could not be quantified in any subject beyond one hour following drug application.

Distribution, excretion and metabolism

Ninety nine percent of a 500ng/mL dose of tafluprost acid is bound to human serum albumin *in vitro*. No studies have been provided that specifically examine the excretion of tafluprost in man. However, tafluprost acid was rapidly eliminated from the circulation and after 30 min the concentrations were below the limit of quantification. Tafluprost is a pro-drug that is rapidly hydrolysed in plasma and different tissues (for example, the cornea) to form tafluprost acid. The latter is responsible for the main pharmacological activity of the drug. Generally the metabolism of tafluprost by human hepatocytes *in vitro* was rapid and extensive. The metabolism did not involve human recombinant CYP450 enzymes.

[13] B, Tajallaei S, Stjernschantz J. Pharmacokinetics of latanoprost in the cynomolgus monkey. 1st communication: single intravenous, oral or topical administration on the eye. *Arzneim-Forsch/Drug Res* 1999;49:225-33.
[14] B, Stjernschantz J. Ocular and systemic pharmacokinetics of latanoprost in humans. *Surv Ophthalmol* 2002; 47(Suppl 1):S6-S12.

Exposure related to safety

Studies examining 0.0001%, 0.0005%, 0.0025% and 0.005% solutions of tafluprost identified that tafluprost caused more ocular (conjunctival) hyperaemia and photophobia than latanoprost (Xalatan®).

Limitations of the PK data

1. Although there was a trend that the pharmacokinetics of the preserved and unpreserved solutions were different, high inter-subject variability render the analysis presented almost redundant and a larger study, comprising a greater number of subjects, should possibly be undertaken to examine the possibility that the two formulations are not bioequivalent.[15]
2. In addition, due to difficulties in detecting tafluprost and tafluprost acid levels in plasma there is very little real PK data available in the evaluation materials.

Although the systemic half-life of tafluprost acid is short, very few studies have examined the PKs of tafluprost in special populations. For instance, the effect of hepatic or renal impairment on the metabolism of tafluprost has not been examined, even though the major metabolic pathway is via the hepatocytes.[16]

1. Therefore precautions/warnings should be included in the PI regarding the prescription tafluprost to patients with hepatic impairment. Similarly, no studies have examined the effect of age (in geriatric or paediatric populations) on the PKs of tafluprost. Results from Study **77551** may suggest that there are differences in the metabolism of tafluprost acid between male and female subjects which may need further investigations (population pharmacokinetics based on Phase III trials).[17]

Drug interactions

No studies examined the interaction of tafluprost with other drugs. Systemic concentrations of tafluprost acid following dosing are low and cytochrome p450 (CYP) enzymes are not involved in its metabolism. It is unlikely to interact with other drugs in man.

Pharmacodynamics

The pharmacodynamics of tafluprost were evaluated in eight studies involving 78 healthy subjects, 50 healthy Japanese subjects and 296 patients with elevated IOP from a US population.

[15] The sponsor clarified that Study #77551 was not a bioequivalence (BE) study; a definitive BE study typically is conducted for oral preparations, not topically applied ophthalmic solutions. The sponsor added that proof of systemic BE for two topical ophthalmic products was not warranted and would not provide proof of efficacy (that is, IOP lowering effect), as the pharmacological activity is in the eye.

[16] The sponsor commented (as outlined in the Sponsor's comment to the Clinical Evaluation Report) that, as this product is intended for ocular use and acts locally without systemic effects, the pharmacokinetics of tafluprost in special populations (hepatic/renal insufficiency) were not examined The sponsor added thatthe Product Information includes a statement that tafluprost has not been studied in these populations and therefore must be used with caution.

[17] The sponsor commented (in their response to the Clinical Evaluation Report) that as Saflutan is intended to exert its pharmacological effect locally, and not systemically, population pharmacokinetic study is not appropriate. The sponsor believes that it is more relevant to assess the effect of age and gender on the efficacy, that is, IOP-recuing effect of tafluprost at the clinical endpoints based on pooled Phase II and Phase III clinical data. The sponsor added that results show that IOP response of tafluprost was similar in different age groups (18-40 years; 41-50 years; 51-60 years; 61-70 years; 71-80 years and >80 years) and genders and as the Phase II and Phase III studiespopulation adequately represent the geriatric population, no additional studies were conducted in this age group.

Mechanism of action

Tafluprost acid is a full agonist at and has high affinity for the FP prostanoid receptor (50% inhibitory concentration (IC_{50}) = 0.5 nM; Study PD001)[18]. The potency of tafluprost acid was 12 times higher than that of latanoprost acid in the same test (study PD001)[19]. The activity on other prostanoid receptors was negligible except for the EP3 receptor (Study PD002)[2]. The affinity of tafluprost acid for a range of prostanoid receptors is given in Table 3. Although the mode of action of tafluprost in human subjects has not been studied, in a nonclinical study performed in primates, tafluprost was shown to statistically significantly increase uveoscleral outflow[2] similar to the effect of other FP prostanoid receptor agonists. A moderate increase in outflow facility was also observed. Tafluprost tended to increase the aqueous humour production, an effect which is occasionally seen with other prostaglandins. The clinical result of these actions was to decrease IOP.

Table 3. Prostanoid receptor profile of tafluprost acid based on EC50/IC50 values (Moles/L).

DP	EP_1	EP_2	EP_3	FP	IP	TP
$>1x10^{-6}$	$>1x10^{-6}$	$>3x10^{-5}$	$7x10^{-8}$	$5x10^{-10}$	$>1x10^{-6}$	$>1x10^{-6}$

Primary pharmacology

Pharmacodynamics in healthy volunteers

Study **77551** examined the IOP lowering potential of two formulations of tafluprost (preserved and unpreserved) 0.0015% ophthalmic solution. Mean IOP decreased from Day 1 to Day 8 by 3.50 and 3.64 mmHg for the preserved and unpreserved formulations, respectively.

The pharmacodynamics of four concentrations of tafluprost (AFP-168) eye drops (0.0001%, 0.0005%, 0.0025% and 0.005%) after single and twice daily doses were examined in Study **WW-74450-EU**. Treatment with all four concentrations of tafluprost resulted in statistically significant decreases in IOP relative to placebo, usually achieving maximum effect at 12h post-dose and persisting throughout the two day treatment period (Table 4). The decrease in IOP relative to placebo was significantly greater with the higher 0.0025% and 0.005% concentrations than with the 0.0001% concentration.

The pharmacodynamics of tafluprost (0.0025% and 0.005%) and Xalatan® (0.005%) eye drops after dosing for one week was examined in Study **WW-74452-EU**. The 0.005% tafluprost solution reduced IOP (around 3-4 mmHg) significantly better than placebo on Days 1, 2, 3, 5 and 7, whereas, there was no significant difference in IOP between 0.0025% tafluprost solution and placebo treated eyes when change in IOP was measured in mmHg. However, if the results were expressed as percentage change from baseline, then the 0.0025% solution significantly decreased IOP on Days 1 and 8 at +8 hours. Although Xalatan significantly decreased IOP by 3.2 and 2.7 mmHg on Day 7 at 4 and 8 hours, respectively, there was no significant difference in IOP reduction between 0.0025% tafluprost and Xalatan®. By contrast, tafluprost 0.005% reduced IOP significantly better than Xalatan® at Day 1 and 3 of treatment (2.3 – 3.6 mmHg). The proposed marketed dose of tafluprost (0.0015%) was not compared with Xalatan in this study.

[18] Nakajima T, Matsugi T, Goto W, Kageyama M, Mori N, Matsumura Y, et al. New fluoroprostaglandin F2α derivatives with prostanoid FP-receptor agonistic activity as potent ocular hypotensive agents. Biol Pharm Bull 2003;26(12):1691-5.
[19] Takagi Y, Nakajima T, Shimazaki A, Kageyama M, Matsugi T, Matsumura Y et al. Pharmacological characteristics of AFP-168 (tafluprost), a new prostanoid FP receptor agonist, as an ocular hypotensive drug Exp Eye Res 2004: 78: 767-776

The ability of tafluprost (0.0015%) ophthalmic solution to lower IOP was examined in Study 15-005. IOP (Mean±SD) in the right and left eyes was 13.2 ± 2.1 and 13.2 ± 1.7 mmHg, respectively, before treatment on Day 1, and had reduced to 10.5 ± 2.9 and 10.9 ± 2.6 mmHg, respectively, on Day 8 (Table 5).

Table 4. Study WW-74450-EU

Mean Intraocular pressure (mmHg)

		Day 1		Day 2	
	Baseline	12 h	24 h	12 h	24 h
0.0001% (n=16)					
Active	13.2	10.4	12.6	10.4	11.8
Placebo	13.4	11.6	12.7	12.0	12.9
Active – placebo	-0.2	-1.1	-0.1	-1.6	-1.1
p-value	-	NS	NS	0.025	NS
0.0005% (n=15)					
Active	13.1	8.4	10.9	9.5	10.7
Placebo	13.1	10.3	12.3	11.9	12.9
Active – placebo	0.1	-1.9	-1.4	-2.4	-2.1
p-value	-	<0.001	0.008	<0.001	<0.001
0.0025% (n=15)					
Active	12.8	7.3	9.7	7.7	8.2
Placebo	12.5	10.9	13.2	12.0	13.6
Active – placebo	0.3	-3.6	-3.5	-4.3	-5.4
p-value	-	<0.001	<0.001	<0.001	<0.001
0.005%	(n=15)		(n=14)		
Active	13.5	7.6	9.9	8.9	9.4
Placebo	13.7	11.9	14.1	12.5	14.0
Active – placebo	-01.	-4.3	-4.2	-3.6	-4.6
p-value	-	<0.001	<0.001	0.001	<0.001

Statistical method, Paired t-tests; Significance level, 5%
Source: Section 16.1.3, Tables 48-49; NS – Not Significant

Table 5 Study 15-005 Descriptive statistics of intraocular pressure (mmHg).

Visit	Eye	N	MEAN	SD	SE	MIN	MEDIAN	MAX
Screening	Right	19	13.63	2.42	0.56	10.0	14.0	18.0
	Left	19	13.79	1.83	0.42	11.0	14.0	17.0
Day 1	Right	19	13.18	2.14	0.49	10.5	12.5	17.5
	Left	19	13.18	1.66	0.38	11.0	13.0	16.5
Day 8	Right	19	10.45	2.86	0.66	6.0	10.0	18.0
	Left	19	10.87	2.59	0.59	7.0	10.0	18.0
Change (Day 1 - Scr)	Right	19	-0.45	1.57	0.36	-3.5	-0.5	2.0
	Left	19	-0.61	0.99	0.23	-2.5	-0.5	1.0
Change (Day 8 - Scr)	Right	19	-3.18	2.90	0.67	-6.5	-3.0	6.5
	Left	19	-2.92	2.78	0.64	-6.0	-3.0	7.0

Healthy Japanese subjects

The pharmacodynamics of four concentrations of tafluprost eye drops (0.0001%, 0.0005%, 0.0025% and 0.005%) after single and twice daily doses was examined in healthy Japanese volunteers in Study **WW-74451-EU**. Treatment with tafluprost resulted in a statistically significant decrease in IOP relative to placebo at one or two time points with all concentrations except the lowest (Table 6). Usually maximum effect was achieved at 8-12 h post-dose and the effect persisted throughout the two day treatment period. The decrease in IOP relative to placebo was significantly greater with the 0.005% tafluprost concentrations than the 0.0001% concentration.

The pharmacodynamics of tafluprost (0.0025% and 0.005%) eye drops after dosing for one week in healthy Japanese male volunteers was examined in study **WW-74453-EU**. Within treatment analysis showed statistically significant decreases in IOP from baseline for 0.005% tafluprost, in particular, on Day 7. However, the largest statistically significant decrease (4.7 mmHg) was observed on Day 2. Neither 0.0025% tafluprost, nor Xalatan® caused a statistically significant decrease in IOP from baseline. There were no statistically significant differences between tafluprost 0.0025%, 0.005% or placebo and Xalatan® at any time point.

Table 6. Study WW-74451-EU

Mean Intraocular pressure (mmHg)

	Day 1			Day 2	
	Baseline	12 h	24 h	12 h	24 h
0.0001% (n=8)					
Active	11.8	10.1	10.4	10.0	11.7
Placebo	11.5	10.0	10.3	10.0	12.1
Active – placebo	0.3	0.1	0.1	0.0	-0.4
p-value	-	NS	NS	NS	NS
0.0005% (n=8)					
Active	11.5	9.1	10.1	8.9	10.0
Placebo	11.1	9.8	10.6	10.0	10.3
Active – placebo	0.4	-0.6	-0.5	-1.1	-0.3
p-value	-	NS	NS	0.040	NS
0.0025% (n=7)					
Active	11.0	7.3	8.1	8.7	7.9
Placebo	11.4	10.3	10.7	10.7	11.9
Active – placebo	-0.4	-3.0	-2.6	-2.0	-4.0
p-value	-	0.004	NS	NS	0.003
0.005% (n=6)					
Active	11.7	7.2	9.5	8.5	9.5
Placebo	11.7	11.0	12.7	11.5	12.8
Active – placebo	0.0	-3.8	-3.2	-3.0	-3.3
p-value	-	0.018	NS	NS	0.013

Statistical method, Paired t-tests; Significance level, 5%
Source: Section 16.1.3, Tables 48-49; NS – Not Significant

PDs in the target population

Two Phase II dose-finding studies [**P15001** and **P15002**] were performed in US patients with elevated IOP. In both studies, the patients were treated with tafluprost once daily in the evening for four weeks.

In Phase II Study **P15001**, all three tafluprost concentrations (0.001%, 0.0025% and 0.001%) were more effective in reducing IOP than 0.005% latanoprost at 24 hours after dosing, however, they were less effective than 0.005% latanoprost 12-20 hours following dosing. There were no statistically significant differences between 0.005% latanoprost and any of the three tafluprost concentrations (0.001%, 0.0025% and 0.001%) in the reduction of mean diurnal IOP. The percentage of patients with a clinically significant reduction (decrease of at least 20%) in mean diurnal IOP was greater with 0.005% latanoprost than with tafluprost (0.001%, 0.0025% and 0.001%) following 7 and 28 days of treatment.

In another Phase II dose-finding study (P15002), 0.0015% tafluprost was the most effective of the three tafluprost concentrations (along with 0.0003%, and 0.0025%) at lowering IOP in patients with open-angle glaucoma or ocular hypertension following 28 days treatment. In the same study, 0.0015% tafluprost was more effective than timolol in

reducing IOP, but less effective than latanoprost. However, none of these differences were statistically significant.

Relationship between concentration and effect

Healthy subjects

Studies in healthy patients suggest that the decrease in IOP induced by tafluprost was significantly greater with the 0.0025% and 0.005% concentrations than with the 0.0001% concentration (WW-74450-EU). In addition, the 0.005% dose of tafluprost was more effective than the 0.0025% dose (Study WW-74452-EU), suggesting that the IOP lowering ability of tafluprost is dose-dependent.

Target population

Based on two Phase II dose-finding studies [P15001, P15002], which examined 0.0015%, 0.0003%, 0.0025% and 0.005% tafluprost, the optimal balance between efficacy and tolerability with tafluprost administered once daily was achieved with a concentration of 0.0015%. As the side effect profile with this concentration of tafluprost was also favourable, this concentration was selected for the Phase III clinical studies.

Pharmacodynamic interactions with other medicinal products or substances

No clinical pharmacology studies specifically examined the pharmacodynamic interaction of tafluprost with other medicinal products or substances.

Genetic differences in pharmacodynamic response

No clinical pharmacology studies specifically examined the effects of genetic differences of the pharmacodynamics of tafluprost.

Evaluator's overall conclusions on pharmacodynamics

PD in healthy subjects

In healthy non-Japanese and Japanese subjects, tafluprost significantly decreased IOP compared to placebo following one and eight days of treatment. In general, tafluprost reduced IOP in a dose-dependent manner and 0.005% tafluprost reduced IOP significantly better than 0.005% latanoprost or 0.0025% tafluprost.

Deficiencies in the PD evaluation

As with the PK studies, no studies have examined the PDs in special populations or the PD interaction of tafluprost with other commonly administered medications, such as timolol. There is also very little information provided regarding the secondary PDs of the drug.

Efficacy

Introduction

The clinical development program for tafluprost consisted of: 5 Phase I studies, two Phase II dose-ranging clinical studies (15-001, 15-002); one Phase II pilot study (74457); four Phase III studies (74458, 15-003, 74460, 77550); and one open label Phase IIIb study (Study 77552). There were also a number of studies conducted in Japan to support registration in that country. These included one Phase I (850502), one Phase II (850202), and three Phase III clinical studies (850303, 850304, 850305). Only summaries of the

Japanese clinical study reports were provided in the current Australian submission and these studies did not form part of the current clinical evaluation.

The preservative-containing formulation was used in all studies in the clinical development program, except the study comparing formulations with and without preservatives (77550) and the study switching from latanoprost to tafluprost (77552).

Main dose response studies

Study 15-001

Methods

The randomised, double-masked, placebo- and active-controlled, parallel-group, multicentre study (15-001) investigated the dose-response relationship of tafluprost in 152 patients with open-angle glaucoma or ocular hypertension and compared the safety and efficacy of three concentrations of tafluprost ophthalmic solution (0.001%, 0.0025%, and 0.005%) with placebo and 0.005% latanoprost. The proposed dose of 0.0015% tafluprost was not evaluated in this study.

Results

There were 152 subjects enrolled, 93% (142/152) completed the study and 7% (10/152) discontinued early (four subjects discontinued due to adverse events, all were treated with tafluprost). Groups were similar in terms of baseline characteristics; the mean age was 60.1 years, 61% were female and 72% Caucasian. The majority (56%, 85/152) of eyes had POAG, 40% (60/152) had OHT, 3% (4/152) had pigmentary dispersion syndrome and 2% (3/152) had a mixed diagnosis. There were 49/152 (32.2%) subjects with protocol violations (9/30 patients given 0.001%, 8/32 patients given 0.0025%, 8/30 patients given 0.005% tafluprost, 14/30 patients given latanoprost and 10/30 placebo patients) with eight (5%) subjects across all five treatment groups having data excluded from the per protocol (PP) analysis.

On Day 28, the mean IOP was significantly lower in most of the tafluprost treatment groups compared to the placebo group. The exception was the lowest dose, 0.001%, group which had no difference in IOP at 8 p.m. The mean IOP was lowest with the 0.0025% dose. All three concentrations of tafluprost were significantly superior to placebo in lowering IOP from baseline to Day 28 ($p<0.001$). The tafluprost concentrations of 0.001% and 0.0025% were similar at reducing IOP, with results similar to latanoprost. The 0.005% dose was the least effective. The mean diurnal IOP was significantly lower than the placebo group at all follow up visits for all doses of tafluprost and was lowest for the 0.0025% dose. There were no significant differences between the latanoprost and tafluprost groups at any visit. The greatest reduction in mean diurnal IOP occurred with the 0.0025% concentration (-5.29mmHg, -22.7%), while both the 0.001% and 0.005% concentrations were slightly less effective (-5.03mmHg, -19.9% and -4.44mmHg, -19.5% respectively). The maximum IOP lowering effect occurred at 12 hours post instillation (at 8 am). The percentage of patients with a clinically significant reduction (decrease of at least 20%) in mean diurnal IOP, was greater with 0.005% latanoprost (74%) than with tafluprost 0.0025% (67%), 0.001% (52%), or 0.005% (52%) following 28 days treatment.

In this study, tafluprost 0.0025% was associated with greatest reduction in IOP, followed by 0.001% and then 0.005%, and no clear dose response relationship was noted.

Study 15-002

Methods

This randomised, double-masked, active-controlled, parallel-group, multicentre trial assessed three doses of tafluprost (proposed dose of 0.0015% and two other doses, 0.0003% and 0.0025%) and compared them to two active controls – a β-adrenergic

blocking agent (0.5% timolol) and a prostaglandin analogue (0.005% latanoprost) in 144 patients with POAG or OHT.

Results

There were 144 subjects enrolled with 5/144 (3.5%) discontinuing prematurely. Protocol deviations occurred in 51/144 (35.4%) subjects and were slightly higher in the latanoprost treatment group (8/28, 9/30, 11/29, 11/29 and 12/28 in tafluprost 0.003%, 0.0015%, 0.0025%, timolol and latanoprost groups, respectively). There were 11 (7.6%) subjects who had part or all of their IOP data excluded from the efficacy analysis, with four of these in the 0.0025% tafluprost group. The average age was 61.1 years, 59.7% were female, 59.7% Caucasian and 28.5% black, and most (64.9%) had a diagnosis of POAG. Baseline characteristics were similar between groups except for baseline IOP where a statistically significant difference (3.09mmHg) was noted between the 0.0025% tafluprost group and the timolol group at the 4 pm time point (p=0.011). For this reason baseline IOP-adjusted data are presented.

On Day 28, the mean IOP was lowest with the 0.0015% tafluprost group. The maximal IOP-lowering effect was noted by Day 14 of the study and the greatest reduction occurred at the 8 am timepoint. Of the three doses, 0.0015% tafluprost produced the greatest reduction in IOP from baseline to Day 28, followed by 0.0025% and then 0.0003%. When adjusting for baseline IOP, the mean difference between 0.0015% tafluprost and timolol was negative at all four time points on Day 28 (range of –1.31 to –0.19 mmHg). For the other concentrations, the mean difference ranged from –2.58 to +0.64 mmHg for 0.0025% tafluprost and from –0.66 to +0.86 mmHg for 0.0003% tafluprost although none of these differences was statistically significant. The lowest dose, 0.0003% tafluprost was statistically significantly inferior to latanoprost in reducing IOP at two timepoints on Day 28 (Table 7). Using a repeated measurement analysis of covariance (RM ANCOVA), it was found that the relative order of effectiveness in reducing IOP (with estimated mean change in IOP) was 0.0025% tafluprost (-5.10mmHg) which was similar to 0.0003% tafluprost (-5.17mmHg) < timolol (-5.58mmHg) < 0.0015% tafluprost (-6.46mmHg) < latanoprost (-6.60mmHg). The mean difference between tafluprost 0.0015% and latanoprost was 0.14 (95% CI -1.12, 1.40). With timolol the difference was -0.89 (95% CI -2.14, 0.37). As both these confidence intervals (CIs) cross zero, no statistically significant difference was found with the active comparators. A statistically significant difference was noted between 0.0015% and 0.0025% tafluprost with a difference of -1.37 (95% CI -2.65, -0.08). At all four time points on Day 28, 0.0015% tafluprost produced a greater number of clinically significant IOP reductions (decrease from baseline in IOP of at least 20%) compared to either 0.0003% or 0.0025% tafluprost (Table 8).

Table 7. Study 15-002

Time Point	0.0003% AFP-168 − Latanoprost	0.0015% AFP-168 − Latanoprost	0.0025% AFP-168 − Latanoprost
8:00	1.74 (−0.28, 3.76)	0.69 (−0.98, 2.36)	0.82 (−0.88, 2.53)
10:00	1.90 (0.14, 3.65) *	1.16 (−0.74, 3.07)	2.41 (0.52, 4.30) *
16:00	1.90 (0.04, 3.77) *	0.26 (−1.46, 1.99)	0.42 (−1.38, 2.23)
20:00	1.51 (−0.51, 3.53)	0.47 (−1.66, 2.61)	0.77 (−1.67, 3.22)

Mean difference in baseline-adjusted IOP (AFP-168 change from baseline – latanoprost change from baseline) with 95% CI (lower limit, upper limit)
* Lower limit of 95% CI is greater than zero

Of the three tafluprost concentrations tested, 0.0015% showed the greatest effect on lowering IOP with no statistically significant differences with the active controls though absolute measures found this dose more effective than timolol and less effective than latanoprost. The lowest dose, 0.0003% tafluprost, was significantly inferior to latanoprost.

Table 8. Study 15-002. Percentage of subjects with a clinically significant IOP reduction (decrease in IOP of at least 20%) on Day 28.

Time Point	0.0003% AFP-168	0.0015% AFP-168	0.0025% AFP-168	Timolol	Latanoprost
8:00	77.8%	79.3%	76.0%	86.2%	89.3%
10:00	55.6%	62.1%	40.0%	57.1%	78.6%
16:00	44.4%	65.5%	64.0%	42.9%	67.9%
20:00	40.7%	58.6%	56.0%	46.4%	46.4%

Evaluator's comments on the dose ranging studies

Study 15-001 showed that the maximum effective dose was 0.0025% tafluprost. The lowest dose tested (in Study 15-002) was 0.0003% tafluprost which lowered IOP but the mean reduction was significantly inferior to latanoprost. No clear dose response relationship was established for tafluprost. However, the dose of 0.0015% tafluprost was more effective than 0.0025% tafluprost and not statistically different to latanoprost and timolol. These results support the use of 0.0015% tafluprost in the pivotal studies.

Main (Pivotal) studies

Study 74458. Latanoprost Non-Inferiority

Methods

The randomised, double-masked, active-controlled, parallel-group, multinational and multicentre Phase III Study 74458 compared the efficacy and safety of tafluprost 0.0015% eye drops with that of latanoprost 0.005% eye drops in 533 patients with open-angle glaucoma or ocular hypertension. The primary efficacy objective was to show that the IOP lowering effect of tafluprost 0.0015% eye drops was non-inferior to that of latanoprost 0.005% eye drops at the end of 6 months of treatment. Data were reported in a 6 month and a 24 month clinical study report (CSR). The CSR for 12 months was not included in the current Australian submission. The study was conducted in 49 centres in 8 countries (Finland, Sweden, Norway, France, Poland, Germany, Italy and Israel) during 2004 and 2005.

After a washout period of up to four weeks, patients were randomised to receive either of the study treatments for 12 months. This period was later extended to 24 months by Protocol Amendment 2. Visits occurred at Week 2 and 6, and then at Month 3 and then 3 monthly until Month 24. A post study visit occurred 2 to 4 weeks after treatment cessation and during this period medication was chosen by the investigator. Subjects were randomised in a 1:1 ratio between treatment groups. To ensure balanced allocation of prior prostaglandin treatment, randomisation was carried out using permuted blocks for prior prostaglandin users and prostaglandin naïve subjects.

Subjects were treated for 12 months or 24 months (if participating in the extension study) with tafluprost 0.0015% eye drops or commercially available latanoprost (Xalatan® 0.005%). One drop was administered to the affected eye(s) daily in the evening at 8 pm. Tafluprost formulation contained the preservative BAK. Any other ocular medication affecting IOP was prohibited during the primary study though it was allowed after 12 months in the extension study.

Study participants

For inclusion, participants needed to be over 18 years of age with a diagnosis of open-angle glaucoma (either primary open-angle glaucoma, pigmentary glaucoma or capsular glaucoma) or ocular hypertension, have an untreated (after washout) IOP of 22-34 mmHg in at least one eye at 8 am (at baseline) and have a best corrected Early Treatment

Diabetic Retinopathy Study (ETDRS) visual acuity score of +0.6 logMAR (Snellen equivalent of 20/80) or better in each eye. Study exclusion criteria were: pregnancy, breastfeeding or not using reliable contraception; any uncontrolled systemic disease; any ocular surgery including laser procedures within 6 months; IOP >34mmHg in either eye at baseline; anticipated change in chronic therapy that could affect the IOP; hypersensitivity to BAK; use of contact lenses; active external ocular disease; corneal abnormality; anterior chamber angle <Grade 2 according to Schaffer classification; advanced visual field defect; unable to safely discontinue use of ocular hypotensive medications during washout; use of other anti-glaucoma medications during the study; and alcohol or drug abuse.

Outcomes/endpoints and statistical methods

The primary efficacy variable was the change from baseline in the overall diurnal IOP at the end of six months (IOP in the worse eye). The worse eye was the eye with the higher IOP at 8 a.m. on the baseline visit, or the right eye if IOP was the same in both eyes. IOP measurements were conducted at 8 am and 12, 4 and 8 pm on scheduled visit days.

Secondary efficacy variables included: the change from baseline in the overall diurnal IOP at the end of three months; the change from baseline in time-wise IOPs (at three and six months); and the proportion of responders[20] at six months. Safety and tolerability variables were also assessed.

Sample size: Assuming a non inferiority limit of 1.5 mmHg, a standard deviation of 4.5mmHg for the change in IOP and a two-sided Type I error rate of 5%, a sample size of 190 evaluable patients (at least 240 randomised patients) per treatment was required for the study to have a power to 90%. A non inferiority margin of 1.5mmHg was chosen as this is the standard margin used in glaucoma trials.

Statistical methods: The study's alternative hypothesis was that tafluprost 0.0015% was non-inferior to latanoprost 0.005%. The non inferiority limit was set at 1.5mmHg. The primary efficacy analysis, change from baseline to six months in the diurnal IOP, used a repeated measurements analysis of covariance (RM ANCOVA) model which included fixed effects for baseline, pooled centre, treatment, visit and time, and all interactions among treatment, visit and time. The non inferiority of tafluprost 0.0015 % versus latanoprost 0.005 % was evaluated using a two-sided 95% confidence interval obtained from the model. A sensitivity analysis without baseline IOP as a covariate (RM ANOVA) was conducted. Efficacy analysis was based on the intention-to-treat (ITT) and the per protocol (PP) datasets in the worse eye. The dataset included all randomised ITT patients who had received at least one dose of study treatment and had at least one efficacy measurement available.

Results

Participant flow: There were 631 subjects screened with 98 screen failures, the most common of which was IOP too low (n=28) and consent withdrawn (n=20). There were 533 subjects randomised, 269 to tafluprost group and 264 to the latanoprost group. The number of prostaglandin naïve patients was similar in the tafluprost group (54.3%; 146/269) and the latanoprost group (52.3%; 138/264).

There were 498/533 (93.4%) subjects who completed six months of treatment. Of the 35 patients who prematurely discontinued the study, 23 were in the tafluprost group and 12 in the latanoprost group. The most common reasons for discontinuation were patient request (in eight given tafluprost and three given latanoprost), lack of efficacy (seven tafluprost patients and three latanoprost patients) and adverse event (three given tafluprost and two given latanoprost). There were 27 subjects with major protocol

[20] A responder was defined as a patient with a certain reduction of IOP (for example, by 15% with increasing steps of 5%) as compared to baseline or with a certain target IOP value (for example, by 20 mmHg with decreasing steps of 1 mmHg).

deviations affecting the diurnal IOP evaluation, 16 in the tafluprost and 11 in the latanoprost group. Five tafluprost subjects had no efficacy or safety measurements post randomisation and therefore the ITT dataset included 528 subjects. However, there were an additional 17 subjects (9 given tafluprost and 8 given latanoprost) with no IOP measurement data from Month 3 and 6 reducing the number of the primary endpoint ITT efficacy dataset to 511 subjects (95.9%; 255 tafluprost and 256 latanoprost).

Conduct of study: The study protocol was amended three times after initiation. The first protocol amendment updated reporting requirements for serious adverse events (SAEs), specified evaluation of iris colour, eyelashes and lid photographs and added new study centres. The second amendment added the extension study, increasing the study duration from 12 to 24 months. The extension treatment was still masked and aimed to determine long term safety and efficacy. The third amendment added an assessment of corneal thickness at 24 months.

Baseline data: Majority of the patients were Caucasian (99.6%), females (58%) with mean age of 62 years and ocular diagnosis was mainly POAG (approximately 56%) or ocular hypertension (approximately 36%). Baseline demographics and ocular findings were similar between groups. A total of 17 (6.3%) tafluprost patients and 16 (6.1%) latanoprost patients reported ocular baseline symptoms. There were 219 (81.4%) patients in the tafluprost group and 206 (78.0%) patients in the latanoprost group who reported use of ophthalmological medication prior to the study, most of which was anti-glaucoma medication (77.0% and 73.1% respectively). Prostaglandins were used prior to the study in 32.7% and 32.2% and ß-blockers in 29.4% and 30.3% of the tafluprost and latanoprost patients, respectively.

Concomitant medication use was reported in 27.7% of the subjects, the most common being anti-inflammatory and anti-rheumatic products in 6.3% of the tafluprost and 7.6% of the latanoprost groups. Baseline mean IOP was marginally higher in the tafluprost group than the latanoprost group.

Compliance: At Month 6, 94.3% (232/246) of the tafluprost and 95.3% (241/253) of the latanoprost groups reported to have instilled their study medication the previous night within one hour of the scheduled time. The proportion of returned bottles was on average 87.8%; however three centres had lower returns of 35.0%, 42.3% and 66.7%. Subjects from these three centres were excluded from the per protocol sensitivity dataset (472/533).

Primary outcome: The mean IOP and percentage change from the baseline for both treatment groups is presented in Figure 3. This shows a reduction in IOP by Week 2 that was sustained to Month 6. At Month 6, the mean change in IOP at 8 am was -8.05mmHg (-31.0%) in the tafluprost group and -9.16mmHg (-35.9%) in the latanoprost group. In the ITT Efficacy RM dataset (N=511), the estimated overall treatment difference (tafluprost-latanoprost) at 6 months from the RM ANCOVA model was 1.44 mmHg with an upper limit of the 95% CI at 1.84mmHg. This exceeded the predefined non inferiority limit of 1.5mmHg (Table 9). The RM ANCOVA analysis on the PP set also failed to demonstrate non inferiority, as did the sensitivity analysis (RM ANOVA) which found a treatment difference of 1.08 with the upper limit of the 95% CI of 1.56.

Figure 3. Study 74458. The mean (±SD) IOP during the study.

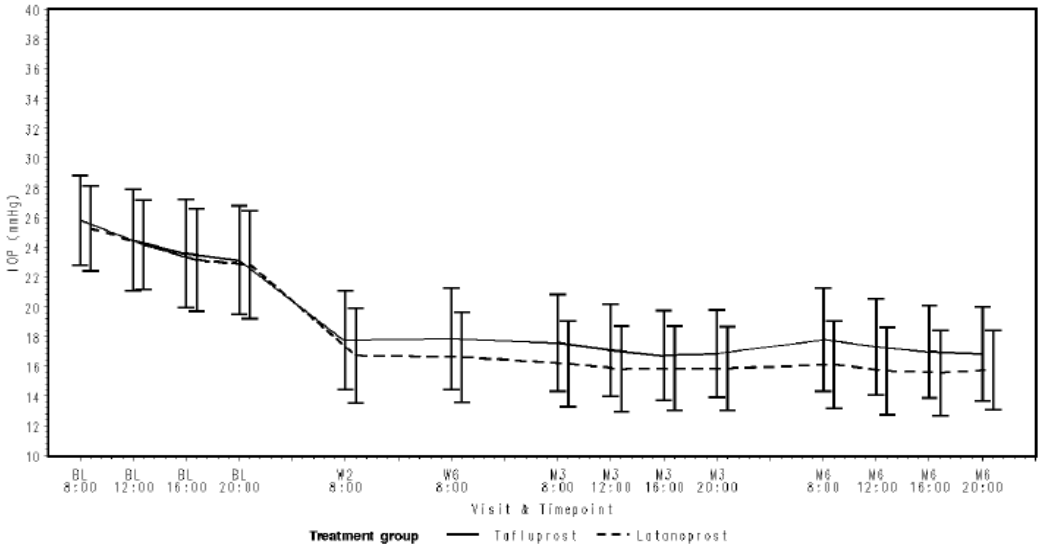


Table 9. Study 74458. The estimated overall treatment difference (tafluprost-latanoprost) at six months.

6 Months	RM ANCOVA		RM ANOVA	
Dataset	Difference	Upper 95% CI	Difference	Upper 95% CI
ITT Efficacy RM (N=511)	1.44	1.84	1.08	1.56
PP Efficacy RM (N=467)	1.29	1.69	0.93	1.41
PP sensitivity RM (N=429)	1.13	1.55	0.70	1.20

Secondary outcomes: Non inferiority at 3 months was not demonstrated in primary analysis (RM ANCOVA) as the treatment difference was 1.15mmHg with the upper 95% CI at 1.55, although the sensitivity analysis (RM ANOVA) did show non inferiority (difference of 0.79mmHg with upper 95% CI 1.26) (Table 10).

The proportion of subjects responding to treatment based on a decrease of ≥20% in the mean diurnal IOP, at 6 months was less in the tafluprost group (than the latanoprost group (80.3% versus 89.9%). The number of subjects with decreases of ≥25% and ≥30% in IOP was also less with tafluprost than latanoprost (62.8% versus 79.0% and 46.4% versus 67.3%, respectively) (Table 11).

Ancillary analyses: Subgroup analysis was conducted for prostaglandin use (users and naïve) and ocular diagnosis (glaucoma and ocular hypertension). Non inferiority was not met for any of these subgroups (Table 12).

Table 10. Study 74458. The estimated overall treatment difference (tafluprost-latanoprost) at 3 months.

3 Months	RM ANCOVA		RM ANOVA	
Dataset	Difference	Upper 95% CI	Difference	Upper 95% CI
ITT Efficacy RM (N=511)	1.15	1.55	0.79	1.26
PP Efficacy RM (N=467)	1.19	1.60	0.85	1.33
PP sensitivity RM (N=429)	1.11	1.54	0.69	1.19

Table 11. Study 74458. Proportion of responders at 6 months, based on decrease in mean diurnal IOP

	Tafluprost (N=239) [1]		Latanoprost (N=248) [2]	
Response criteria	No	Yes	No	Yes
≥15% decrease	23 (9.6%)	216 (90.4%)	14 (5.6%)	234 (94.4%)
≥20% decrease	47 (19.7%)	192 (80.3%)	25 (10.1%)	223 (89.9%)
≥25% decrease	89 (37.2%)	150 (62.8%)	52 (21.0%)	196 (79.0%)
≥30% decrease	128 (53.6%)	111 (46.4%)	81 (32.7%)	167 (67.3%)

Source: Table 14.2.3.2

[1] 25 patients were excluded: one patient (9152) had incomplete data at baseline, 24 patients had incomplete data at Month 6; [2] 16 patients with incomplete data at Month 6 were excluded.

Table 12. Study 74458. Subgroup analysis

ITT Efficacy RM (N=511)	RM ANCOVA		RM ANOVA	
Previous use of prostaglandins	Difference[1]	Upper 95% CI	Difference[1]	Upper 95% CI
Prior prostaglandin users	1.41	2.09	1.30	2.06
Prostaglandin naïve patients	1.37	1.96	0.79	1.45
Ocular diagnosis	Difference[1]	Upper 95% CI	Difference[1]	Upper 95% CI
Glaucoma[2]	1.58	2.17	0.93	1.57
Ocular hypertension	1.06	1.74	1.16	1.98

Source: Appendix 16.1.9

[1] tafluprost-latanoprost at 6 months; [2] Open-angle, capsular or pigmentary glaucoma

Study 74458. 24 month data

For the extension study, the same masked treatment was continued as per initial randomisation. During the extension study the investigator could add other IOP lowering therapies if judged necessary. There were no formal statistical hypotheses for the 24 month data. Efficacy analysis methodology was the same as the initial study. Analysis included the change from baseline in diurnal IOP at 18 and 24 months and the proportion of responders at 24 months, as well as assessment of non inferiority to latanoprost (with a treatment difference limit of 1.5mmHg). Both the ITT and PP datasets were analysed.

Of the initial 533 randomised subjects, 476 (229 tafluprost and 247 latanoprost) completed 12 months, 420 agreed to continue a further 12 months and 402 (185 tafluprost and 217 latanoprost) completed 24 months of treatment. This means 10.7% of subjects discontinued in the first 12 months and 4.3% in the second 12 months. The main reason for discontinuation between 12 and 24 months was lack of efficacy (5 tafluprost, 0 latanoprost) and adverse events (one given tafluprost and two given latanoprost after 24 months). The tafluprost AE was asthenopia and visual field defect The ITT dataset for 24 months included 419 (195 tafluprost and 224 latanoprost) subjects with 409 subjects in the ITT RM ANCOVA and the PP efficacy dataset included 401 (187 tafluprost and 214 latanoprost) subjects.

The mean IOP during the study up to Month 24 is summarised in Figure 4 and shows a sustained effect on IOP reduction which was slightly greater with latanoprost. The estimated overall treatment difference (tafluprost-latanoprost) was 1.20 mmHg with RM ANCOVA (upper 95% CI: 1.52 mmHg, which exceeded the predefined non-inferiority limit of 1.5 mmHg) and 0.95 mmHg with RM ANOVA (upper 95% CI: 1.38 mmHg, which met the predefined definition of non-inferiority). As in the first 6 months of treatment, non inferiority of tafluprost was not confirmed on the adjusted model. This was also the case on the PP efficacy dataset (difference 1.06, upper 95% CI 1.54). Overall, fewer tafluprost subjects than latanoprost patients had responded to treatment at 24 months (IOP decrease of ≥25%: 65.2% versus 75.4% respectively) (Table 13). Results for subgroup analysis (prostaglandin users or naïve and glaucoma and ocular hypertension) were similar to the six month data and no group was found to meet the non inferiority criteria.

Figure 4. Study 74458, 24 month extension. The mean (±SD) IOP during the study.

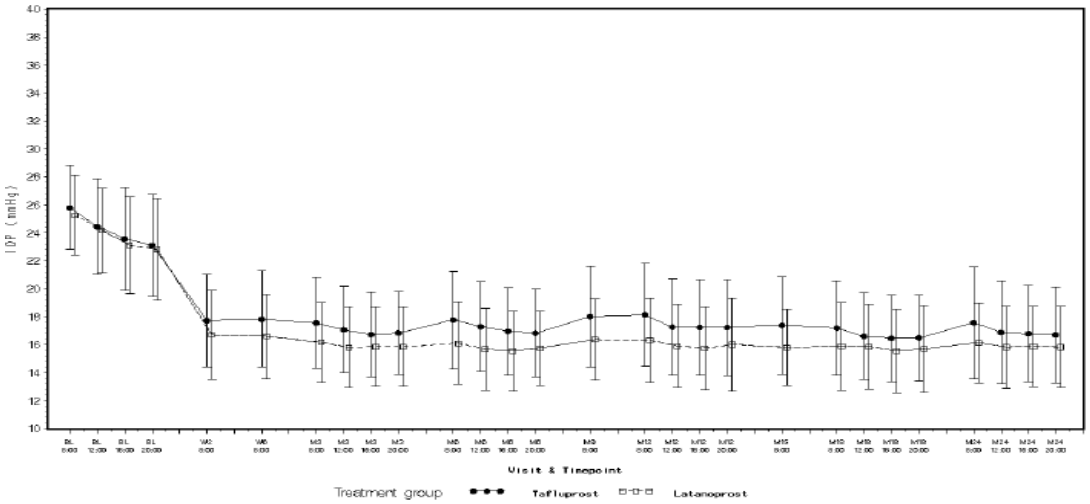


Table 13. Study 74458, 24 month extension. Proportion of responders at 24 months (based on decrease in mean diurnal IOP).

	Tafluprost (N=181) [1]		Latanoprost (N=211) [2]	
Response criteria	No	Yes	No	Yes
≥15% decrease	28 (15.5%)	153 (84.5%)	17 (8.1%)	194 (91.9%)
≥20% decrease	46 (25.4%)	135 (74.6%)	25 (11.8%)	186 (88.2%)
≥25% decrease	63 (34.8%)	118 (65.2%)	52 (24.6%)	159 (75.4%)
≥30% decrease	90 (49.7%)	91 (50.3%)	88 (41.7%)	123 (58.3%)

Source: Table 14.2.2.4

[1] 14 patients with incomplete or no data at Month 24 were excluded.

[2] 13 patients with incomplete or no data at Month 24 were excluded.

Efficacy summary

The IOP lowering effect was greater with latanoprost and the primary endpoint was not met at any timepoint through to 24 months[21]. The non inferiority limit of 1.5mmHg in the treatment difference was crossed by the upper limit of the 95% CI in the primary analysis (ITT and PP set) and in the sensitivity analysis (ITT dataset). Non inferiority was only found using the RM ANOVA PP dataset which did not adjust for baseline IOP. These results are less reliable since there were differences between groups in baseline IOP. An IOP reduction of 20-30% is clinically relevant and at this level there were fewer responders with tafluprost than with latanoprost.

Study 15-003. Timolol Non-Inferiority

Methods

Study 15-003 was a randomized, double-masked, parallel-group, multicenter, 12-month trial comparing the efficacy and safety of tafluprost 0.0015% with timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension. As in Study 74458, the hypothesis was that once daily tafluprost was non-inferior to twice daily timolol.

This study was conducted in 2004 and 2005 at 26 centres in the USA. The study duration was 12 months and results were reported in two clinical study reports; one for the first six months of data and one for the full 12 months. The design and methodology for the study was the same as for Study 74458 with a wash out from previous medication, randomisation and 12 months of masked treatment with the same visit schedule. Subjects were randomised to the tafluprost and timolol groups in a 3:2 ratio using an interactive

[21] The sponsor commented that non inferiority was demonstrated at Months 3 and 18. Upper limits of 95% CI were 1.46 and 1.49 mmHg, respectively.

voice response system (IVRS). Subjects received either tafluprost 0.0015% once a day or timolol maleate 0.5% twice a day. Tafluprost subjects also received the vehicle of tafluprost solution in the morning. Tafluprost solution contained BAK preservative. The same treatment regimen continued for 12 months.

The study was double masked and study bottles were identical and marked for 'morning' or 'evening' administration. Morning and evening medications were in different colour packages. Three subjects were unblinded during the study due to SAEs.

Study participants: Inclusion and exclusion criteria were the same as Study 74458 with the addition of excluding subjects contraindicated to beta-blocker therapy.

Outcomes/endpoints and statistical methods

As in Study 74458, the change from baseline in the overall diurnal IOP at Month 6 was the primary efficacy variable. IOP measurements were taken 3 times a day (8 and 10 and 4 pm) rather than four times a day. Following FDA discussions, a primary endpoint was added of IOP at each time point at each visit through to Month 6. Secondary efficacy endpoints were the same as Study 74458.

The sponsor assumed that the change in IOP would be larger with tafluprost than with timolol, and therefore the difference set for sample size calculations was 1.6mmHg. Assuming a standard deviation of 4.5mmHg for the change in IOP, Type I error rate of 5% and 90% power, a sample of 170 evaluable patients (216 randomised) per treatment group were necessary. Allocation of 3:2 was chosen, reportedly to increase the number of subjects exposed to tafluprost. The planned randomised numbers for tafluprost and timolol were 270 and 180, respectively.

Statistical methods were the same as Study 74458. The non inferiority limit was set at 1.5mmHg with the addition of primary efficacy analysis including the examination of two-sided 95% CI for the difference in IOP between treatments at each visit to Month 6. Non inferiority to timolol was judged if the upper limit of this CI did not exceed 1.5mmHg at all time points and did not exceed 1.0mmHg at the majority of time points.

Results

Participant flow: There were 591 screened subjects with 458 randomised (267 to tafluprost and to 191 timolol). Prior prostaglandin use was higher than in Study 74458; 71.2% and 72.8% of patients in the tafluprost and timolol groups, respectively. There were 40 subjects who prematurely discontinued, 17/267 (6.4%) in the tafluprost group and 23/191 (12.0%) in the timolol group; The most common reasons being adverse events (six given tafluprost and nine given timolol) and lack of efficacy (four given tafluprost and seven given timolol). Of the six tafluprost subjects with AEs resulting in discontinuation, four had ocular symptoms (mainly hyperaemia and irritation), one had headache and one had unrelated cardiac failure, acute renal failure and hypertension.

There were 23 tafluprost and 10 timolol subjects with a major protocol deviation affecting the Month6 IOP evaluation and 55 (20.6%) tafluprost and 31 (16.2%) timolol subjects with deviations affecting IOP data through the 6 months of the study. This incidence is slightly higher in the tafluprost group and the main protocol deviation was the use of prohibited concomitant medications.

The ITT efficacy dataset included 452 patients and the PP efficacy dataset included 450 subjects. Since the Month 3 and 6 data were needed for the RM ANCOVA analysis, the ITT dataset for this analysis included 437 evaluable subjects (257 tafluprost and 180 timolol) and the PP dataset included 390 subjects (228 tafluprost and 162 timolol).

Conduct of study: The protocol was amended once following feedback from the FDA. This included five additional IOP measurements at scheduled visits as well as an additional primary endpoint and its statistical methods.

Baseline data: Baseline data was similar between groups. The mean age of subjects was 61.3 years, 59.2% were female (7.4% were of childbearing potential), 62.5% Caucasian and 24.0% black. Ocular diagnosis was predominantly POAG (55.0%) and OHT (43.0%). Iris colour and mean corneal thickness were similar between groups as was gonioscopy (anterior chamber angle) evaluation with most eyes being Grade 3[22] (43%) or 4 (51%). The most common prior medical conditions were ocular in 265 patients (99.3% tafluprost, 100.0% timolol), cardiovascular (59.2% tafluprost, 64.4% timolol) and musculoskeletal (57.7% tafluprost, 61.8% timolol). Anti-glaucoma medication was used in 54.3% and 60.2% of the tafluprost and timolol groups, respectively, prior to the study. Concomitant medications were used in 61.0% of the tafluprost and 57.1% of the timolol group during the study, the most common being analgesics, antibacterials and anti-inflammatories.

Compliance: Compliance was measured by direct questioning at subject visits and it was similar between groups. At Month 6, 93.6% of the tafluprost group and 96.5% of the timolol group reported instilling study medication within 1 hour of the scheduled time.

Primary outcome: At the six months morning (8 am) timepoint, there was a mean change of -6.58mmHg (-25.4%) in the tafluprost group and -6.45mmHg (-25.2%) in the timolol group. A treatment effect was evident at Week 2 and it was maintained for 6 months. Non inferiority to timolol was demonstrated with the treatment difference of -0.28mmHg and the upper limit of the 95% CI being 0.21mmHg. This was supported by the PP analysis (Table 14).

Table 14. Study 15-003. The estimated overall treatment difference (tafluprost – timolol) at 6 months.

6 Months	RM ANCOVA		RM ANOVA	
Dataset	Difference	Upper 95% CI	Difference	Upper 95% CI
ITT Efficacy RM (N=437)	-0.28	0.21	-0.27	0.29
PP Efficacy RM (N=390)	-0.19	0.30	-0.24	0.32

The additional primary endpoint analysis of comparisons of IOP at all timepoints at each study visit found the upper limit of the 95% CI did not exceed 1.5mmHg at any timepoint and only exceeded 1.0mmHg on one occasion in the PP efficacy analysis (Table 15).

Secondary outcomes: Non inferiority to timolol was also demonstrated on the change from baseline in diurnal IOP to Month 3 (difference of -0.27mmHg, upper limit 95% CI 0.22) and also for time wise comparison at 3 and 6 months. The proportion of responders, based on decrease in mean diurnal IOP, was also similar between groups at 6 months with 78-82% showing >15% reduction in IOP from baseline.

Ancillary analyses: Subgroup analysis for prior prostaglandin users, prostaglandin naïve patients, glaucoma and ocular hypertension confirmed non inferiority of tafluprost to timolol for all groups.

[22] Shaffer classification: Grade 4, wide open (35º-45º); Grade 3, moderately open (25º-34º); Grade 2, moderately narrow (20º); Grade 1, very narrow (10º); Grade 0, closed (0º).

Table 15. Study 15-003. Time wise comparisons of IOP

Visit	Time	ITT Efficacy	ITT LOCF	PP Efficacy
Week 2 [3]	8:00	-0.50 [0.13][1]	-0.50 [0.13]	-0.55 [0.09]
	10:00	-0.22 [0.77]	-0.22 [0.77]	-0.18 [0.85]
	16:00	-0.31 [0.68]	-0.31 [0.68]	-0.40 [0.64]
Week 6 [3]	8:00	-0.08 [0.56]	-0.17 [0.46]	0.18 [0.86]
	10:00	-0.19 [0.60]	-0.18 [0.61]	0.17 [1.05]
	16:00	-0.74 [0.07]	-0.70 [0.11]	-0.52 [0.38]
Month 3	8:00	-0.36 [0.34]	-0.51 [0.20]	-0.42 [0.31]
	10:00	-0.12 [0.52]	-0.11 [0.53]	-0.25 [0.42]
	16:00	-0.38 [0.22]	-0.37 [0.24]	-0.40 [0.23]
Month 6	8:00	-0.01 [0.68]	-0.22 [0.48]	-0.02 [0.69]
	10:00	-0.06 [0.59]	0.03 [0.71]	0.03 [0.68]
	16:00	-0.85 [-0.27][2]	-0.78 [-0.17][2]	-0.74 [-0.15][2]

[1]Difference (tafluprost-timolol) and the upper limit of the 95% CI for the difference
[2]Statistically significant difference in favour of tafluprost
[3]The number of patients is smaller at 10:00 and 16:00 time points (see table 6.1for details)

Study 15-003: 12 month data

Of the 458 subjects randomised (267 tafluprost and 191 timolol), 418 (91.3%) completed 6 months of treatment (250 tafluprost and 168 timolol) and 402 (87.8%) completed 12 months of treatment (240 tafluprost and 162 timolol). Of the 10 tafluprost subjects who prematurely discontinued between 6 and 12 months, two were for AEs, one lack of efficacy, three withdrew consent, three were lost to follow up and there was one pregnancy (a healthy child was subsequently delivered). The ITT efficacy dataset included 412 subjects (247 tafluprost, 165 timolol) and the ITT dataset for the RM ANCOVA included 402 subjects (240 tafluprost and 162 timolol).

IOP lowering effect of both treatments was maintained from 6 to 12 months (Figure 5). Based on the change from baseline to 12 months in the diurnal IOP, the overall treatment difference (tafluprost-timolol) was 0.43mmHg, with the upper limit of the 95% CI at 0.43 indicating that tafluprost remained non-inferior to timolol. This was confirmed on the PP analysis. Time wise comparisons up to Month 12 found the upper limit of the 95% CI for the difference between treatments was below 1.5mmHg on all occasions and above 1.0mmHg at one additional timepoint (8 am, Month 12). The proportion of responders remained similar between treatment groups and similar to that seen at 6 months (Table 16). Non inferiority was demonstrated in the subgroup analysis at 6 and 12 months.

Figure 5.Study 15-003, 12 month data. The mean (±SD) IOP during the study

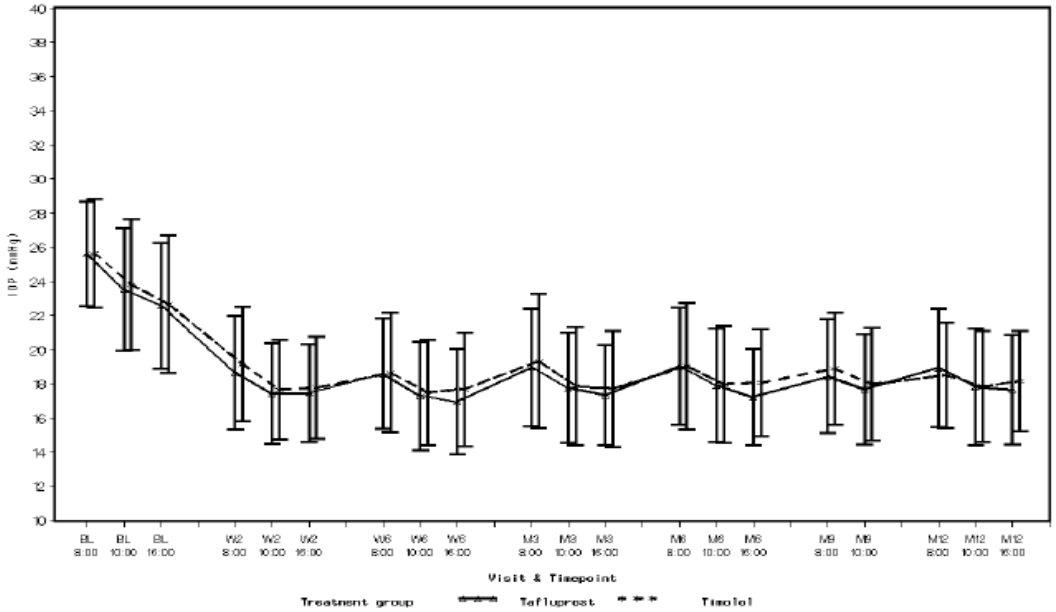


Table 16. Study 15-003, 12 month data. Proportion of responders at 12 months (based on decrease in mean diurnal IOP)

	Tafluprost (N=239) [1]		Timolol (N=159) [2]	
Response criteria	No	Yes	No	Yes
≥15% decrease	47 (19.7%)	192 (80.3%)	31 (19.5%)	128 (80.5%)
≥20% decrease	89 (37.2%)	150 (62.8%)	51 (32.1%)	108 (67.9%)
≥25% decrease	136 (56.9%)	103 (43.1%)	97 (61.0%)	62 (39.0%)
≥30% decrease	176 (73.6%)	63 (26.4%)	125 (78.6%)	34 (21.4%)

Source: Table 14.2.2.4
[1] 8 patients with incomplete or no data at Month 12 were excluded.
[2] 6 patients with incomplete or no data at Month 12 were excluded.

Efficacy summary

Tafluprost demonstrated IOP lowering effects that were maintained for the 12 months of treatment. Non inferiority to timolol was found on the ITT and PP analysis and also by the criteria set by the FDA which included analysis at each timepoint during the 12 months of the study. Secondary endpoints and subgroup analyses confirmed the primary efficacy results.

Study 74460. Adjunctive Therapy with Timolol.

Methods

The randomised, double-masked, placebo-controlled, parallel-group, multinational and multicentre Phase III Study 74460 evaluated the efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy with timolol 0.5% eye drops in 185 patients with open-angle glaucoma or ocular hypertension who are only partially controlled with timolol treatment. The primary hypothesis for efficacy was to show that the IOP lowering effect of tafluprost is superior to that of vehicle eye drops when used adjunctively with timolol 0.5% at the end of a 6-week randomised treatment period. Subjects were randomised into one of the two treatment groups using randomly permuted blocks separately for each study centre. The tafluprost/vehicle treatment was double masked.

During the four week run in period, subjects received timolol maleate 0.5% eye drops twice daily (at 8 am and 8 pm) into the affected eye(s). Subjects were then randomised for

the six week treatment period to either: timolol 0.5% one drop twice daily (at 8 am and 8 pm) and tafluprost 0.0015% one drop once daily (8.10 pm) in the affected eye(s); or timolol 0.5% twice daily (at 8 am and 8 pm) and vehicle once daily (8.10 pm) in the affected eye(s). Only the tafluprost/vehicle drops were masked. During the 6 week extension period the treatment was open label with tafluprost 0.0015% once daily (at 8.10 pm) and timolol 0.5% twice daily (at 8 am and 8 pm) in the designated eye(s). The tafluprost formulation used contained preservative (BAK). The vehicle formulation was identical except for the tafluprost component.

Study participants

Inclusion criteria were similar to the other Phase III studies: age 18 years or more, diagnosis of open angle glaucoma or ocular hypertension; IOP of 22-30mmHg in at least one eye in at least one measurement at the baseline visit (when only treated with timolol 0.5% eye drops twice daily for at least 4 weeks); best corrected ETDRS visual acuity score of +0.6logMAR or better in each eye.

The exclusion criteria were: previous use of any prostaglandins; uncontrolled systemic disease; contraindications to beta-blocker therapy; IOP >30mmHg at any time point in either eye at baseline; use of contact lenses; filtration surgery at any time or other surgery within 6 months; active external ocular disease; any other ocular condition that may interfere with the study; corneal abnormality; anterior chamber angle < Grade 2; advanced visual field defect; use of any anti-glaucoma medications other than the study ones; change in chronic therapy that could affect the IOP; hypersensitivity to the study medications or BAK; alcohol or drug abuse; pregnancy, lactation or not using reliable contraception for women of child bearing potential.

The main difference to the other Phase III studies was that all subjects were prostaglandin naïve.

Outcomes/endpoints and statistical methods

Primary efficacy variable was the change from baseline in the overall diurnal IOP at six weeks. The primary evaluation of IOP was based on the worse eye and diurnal measurements were done at 8 and 10 am and 4 pm. The secondary efficacy variables were: change from baseline in time-wise IOPs (8 and 10 am and 4 pm) at six weeks; change from baseline in the overall diurnal IOPs and time wise IOPs (8 and 10 am and 4 pm) at Weeks 2 and 4; and proportion of responders at six weeks. In addition, efficacy variables for the extension period were: change from baseline in the overall diurnal IOP at 12 weeks; change from baseline in time-wise IOPs (8 and 10 am and 4 pm) at 12 weeks; and the proportion of responders at 12 weeks.

In order to detect a difference of -2.0 mmHg between tafluprost and vehicle (placebo), assuming a standard deviation of 4.0 mmHg for the change in IOP, a two-sided Type I error rate of 5% and a power of 90%, the study required a sample size of 85 evaluable patients (at least 100 randomised patients) per treatment group.

The alternative hypothesis was that tafluprost 0.0015% was superior to vehicle when used adjunctively with timolol 0.5%. Superiority was shown if the upper limit of the 95% CI for the difference (tafluprost versus vehicle) was below 0 mmHg. Analysis was based on the ITT dataset and also the PP dataset. The RM ANCOVA model was used as in the other Phase III studies. The sensitivity analysis (RM ANOVA) did not include baseline IOP as a covariate. The treatment difference, 95% CI for the difference and p value were calculated from the model.

Results

Recruitment: The study was conducted between April 2005 and February 2006 at ten centres in four countries (Russia, Ukraine, Estonia and Latvia).

Participant flow: There were 226 subjects screened, 41 screen failures, and 185 subjects randomised (96 timolol+tafluprost and 89 timolol+vehicle group). Of these, 175 completed six weeks of treatment (90 tafluprost and 85 vehicle) and 171 completed the further 6 weeks extension on tafluprost. For the 14 subjects who prematurely discontinued the most common reason was an AE (four tafluprost subjects and one vehicle), lack of efficacy (three vehicle), patient request (two tafluprost and three vehicle) and improper study entry (one tafluprost). The AEs leading to discontinuation for tafluprost were blurred vision with pruritus, tinnitus and vertigo, two cases of allergic conjunctivitis and one stroke leading to death.

There were 17 subjects with major protocol deviations (nine tafluprost and eight vehicle) impacting on the Week 6 diurnal IOP evaluation. Most deviations were a study visit occurring outside the scheduled time window.

Numbers analysed: At 6 weeks, ITT dataset, and the ITT dataset for the RM ANCOVA, included 181 subjects (four subjects had no post baseline IOP measurements) (93 tafluprost and 88 vehicle). The PP efficacy dataset at 6 weeks for the RM ANCOVA included 160 subjects (83 tafluprost and 77 vehicle).

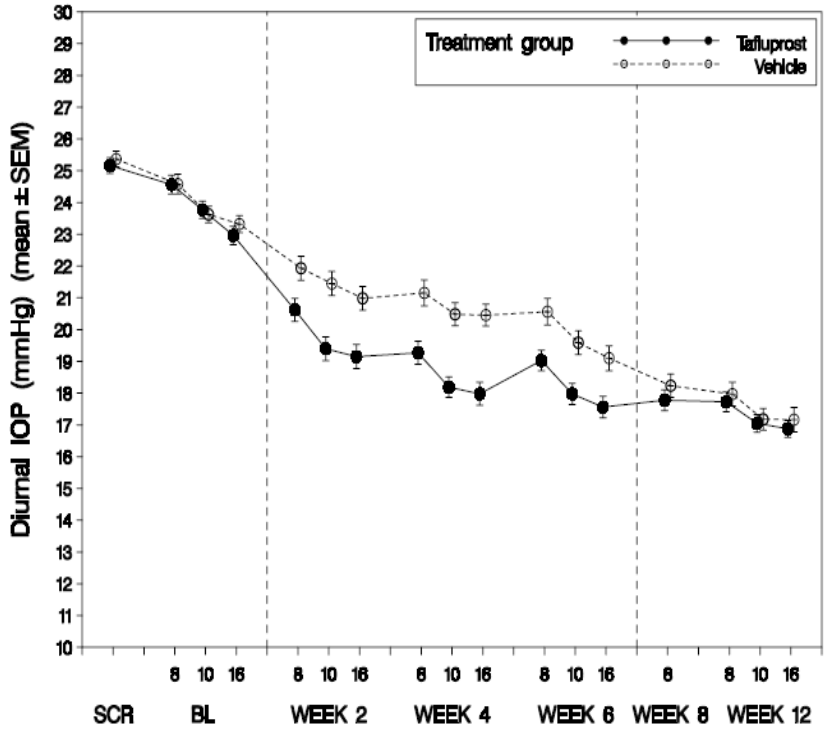
Conduct of study: There was one protocol amendment which was implemented prior to study initiation. This included the enrolment of prostaglandin naïve subjects.

Baseline data: The mean age of participants was 66.3 years in the tafluprost group and 68.0 years in the vehicle group. The tafluprost group had more women (59.4%) compared to the vehicle group (52.8%). All subjects were Caucasian. Ocular diagnosis was similar between groups, with 79.5% having POAG, 7.7% capsular glaucoma and 4.3% with OHT. Iris colour was similar between groups. The anterior chamber angle of eyes on gonioscopy evaluation was predominantly Grade 3 (69.8% tafluprost, 78.7% vehicle). However the incidence of Grade 4 severity was higher in the tafluprost group than in the placebo group (20.8% tafluprost, 11.2% vehicle). Eye disorders other than the study indication (54.2% tafluprost, 65.2% vehicle) and vascular disorders (45.8% tafluprost, 43.8% vehicle) were the most frequently noted medical conditions at baseline. Topical beta-blockers had been used in 91.7% of the tafluprost group and 96.6% of the vehicle group prior to the study. At baseline, the mean IOP in the worse eye was comparable between groups.

Compliance: Compliance was assessed by questioning the subjects at study visits. At Week 6, 100% of subjects in both treatment groups reported to have instilled both eye drop treatments the previous evening. There was no summary data on returned drug supplies in the CSR.

Primary outcome: Post baseline IOP measurements are presented in Figure 6. By Week 6, there was a 21.9 to 24.0% reduction in the mean IOP in the tafluprost group compared to a 15.9 to 17.5% reduction in the vehicle group. At week 12, the percentage reduction was 26.2%-27.8% in the tafluprost group and 25.9%-26.8% in the vehicle group. At Week 6, the overall treatment difference (tafluprost-vehicle) was -1.49mmHg with the upper limit of the 95% CI at -0.66mmHg ($p<0.001$) suggesting statistical superiority. Superiority was also seen on the PP analysis and the sensitivity analysis (Table 17).

Figure 6. Study 74460. The mean (±standard error) diurnal IOP during the study



SCR = Screening; BL = Baseline

Table 17. The estimated overall treatment difference (tafluprost – vehicle) at 6 weeks

Week 6	RM ANCOVA			RM ANOVA		
Dataset	Difference	Upper 95% CI	P-value	Difference	Upper 95% CI	P-value
ITT efficacy RM-R (N=181)	-1.49	-0.66	<0.001	-1.54	-0.69	<0.001
PP efficacy RM-R (N=160)	-1.54	-0.72	<0.001	-1.63	-0.75	<0.001

Secondary outcomes: Superiority was demonstrated after two and four weeks in the change from baseline in the overall diurnal IOP; the difference at 2 weeks was -1.65 (upper 95% CI: -0.82) and at 4 weeks was -2.20 (upper 95% CI: -1.37). Superiority was also found at each timepoint (8 and 10 am and 4 pm) at 2, 4 and 6 weeks ($p<0.05$ for all points).

At 12 weeks, after the vehicle subjects had been switched to tafluprost for 6 weeks, the estimated overall treatment difference was -0.09 (upper 95% CI: 0.62, p=0.81) indicating that the groups had reached similar IOP levels. The proportion of responders was also similar between groups at 12 weeks (Table 18).

Table 18. Study 74460. Proportion of responders at 12 weeks (based on decrease in the mean diurnal IOP).

Response criteria	Tafluprost (N=90)[1,3]				Vehicle (N=82)[2]			
	No		Yes		No		Yes	
	N	%	N	%	N	%	N	%
≥15% decrease	13	14.4	77	85.6	11	13.4	71	86.6
≥20% decrease	23	25.6	67	74.4	24	29.3	58	70.7
≥25% decrease	36	40.0	54	60.0	36	43.9	46	56.1
≥30% decrease	52	57.8	38	42.2	54	65.9	28	34.1

Source: Table 14.2.5.2

[1] 4 patients with incomplete data at Week 12 were excluded.
[2] 5 patients with incomplete data at Week 12 were excluded.
[3] Tafluprost patient 2203 discontinued the study soon after the 12-week visit, and thus had IOP data at Week 12.

Subgroup analyses were not conducted as all subjects were prostaglandin naïve and there were only eight subjects with ocular hypertension.

Efficacy summary

The combination therapy of tafluprost and timolol showed statistically significant greater lowering of IOP compared to tafluprost and vehicle (treatment difference of 1.49mmHg (upper limit of the 95% CI being -0.66mmHg, $p<0.001$). These results were robust and confirmed in the PP dataset and the sensitivity analysis. Superiority was found at all timepoints. On switching from vehicle to tafluprost in the extension period, the vehicle subjects reached similar IOP level as the tafluprost group.

Study 77550. Preservative-containing and preservative-free equivalence

Methods

The randomised, investigator-masked, multicentre, cross-over Phase III Study 77550 compared pharmacodynamics of the preservative-containing and preservative free formulations of tafluprost 0.0015% eye drops in 43 patients with open-angle glaucoma or ocular hypertension. The primary aim of this study was to show that IOP reduction was equivalent for the two formulations at the end of the 4-week treatment period. The duration of the treatment periods was four weeks. The first treatment period was preceded by a washout period, the length of which was determined by the prior medication. The second treatment period was preceded by a four week washout period. A post study visit occurred 1 to 3 weeks after treatment Period 2.

Results

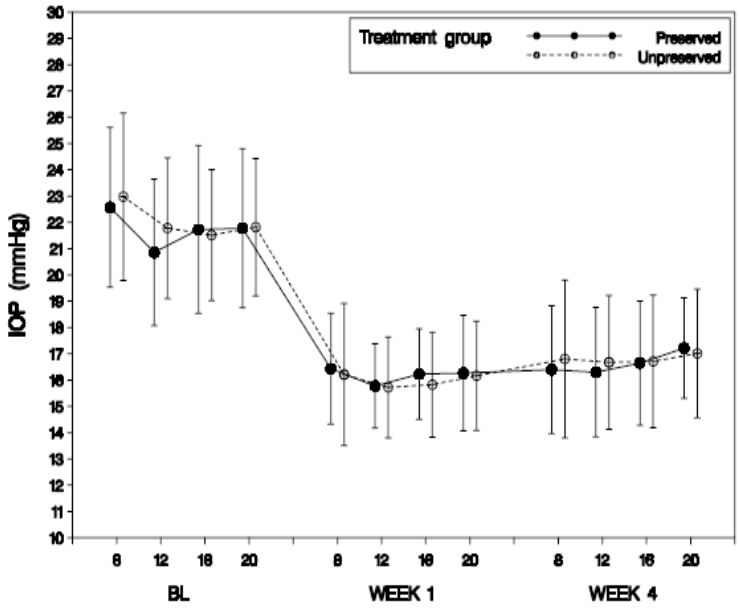
Participant flow: There were 45 subjects screened, two failed the screen and 43 were therefore randomised for study (21 in the preserved-unpreserved sequence and 22 in the unpreserved-preserved sequence). One subject discontinued the study due to lack of efficacy and 42 completed the study. There was one major protocol violation. The ITT dataset for efficacy included 43 patients and the PP dataset 41 subjects.

Baseline data: The mean age was 65.3 years, 62.8% were female and all were Caucasian. Most subjects had POAG (62.8%) followed by OHT (31.4%) and capsular glaucoma (4.7%). Most eyes had an anterior chamber angle of 3 (80%), cataracts were present in 32.6% of subjects, vascular disorders in 25.6% and metabolism and nutrition disorders in 20.9%. All subjects were using ophthalmological medications prior to the study: 93% used prostaglandin analogues, 20.9% carbonic anhydrase inhibitors (CAIs) and 18.6% beta blockers.

Compliance: Compliance based on subject report was high with only one of 43 subjects reporting an error with drop instillation the night prior to a study visit.

Primary outcome: IOP lowering was seen by Week 1 and continued to Week 4 (Figure 7). The overall treatment difference (unpreserved-preserved) at four weeks on RM ANCOVA model (ITT dataset) was 0.01mmHg (95% CI: -0.46, 0.49, $p=0.96$). For the PP efficacy dataset the difference was -0.05 (95%CI: -0.52, 0.42, $p=0.83$). The 95% CIs for the difference were within the preset equivalence range (-1.5 to 1.5mmHg). The sensitivity analysis (RM ANOVA, ITT dataset) also confirmed equivalence (difference -0.12, 95% CI -0.95, 0.71).

Figure 7. Study 77550. The mean (SD) IOP during the study in the worse eye



BL = Baseline

Secondary outcomes: Time wise comparisons at Week 1 and 4 found equivalence at all timepoints.

Clinical studies in special populations and Analysis performed across trials (pooled analysis and meta-analysis)

There were no studies in special populations or pooled analyses or meta-analyses included in the current Australian submission.

Supportive studies

Study 74457. Pilot Phase II

In the pilot Phase II Study 74457 involving 38 patients with POAG/OHT, the IOP lowering effect of tafluprost 0.0015% was reached after 7 days and was comparable to that of latanoprost 0.005% (-9.55mmHg for tafluprost and -8.82mmHg for latanoprost). IOP reduction was maintained until 36 hours post dose and therefore supported once daily dosing. The IOP remained stable on Day 42 (last dose at 10 pm on Day 41) and started to increase in both groups on Day 43 (36 hours after the last dose) (Figure 8). The estimated overall treatment difference (tafluprost-latanoprost) was 0.056 mmHg (95% CI: -1.497 to 1.608 mmHg, p=0.942). The proportion of responders on Day 42, based on decrease in mean diurnal IOP, was comparable between groups (Table 19).

Figure 8. Study 74457. The mean (±SD) IOPs in the worse eye

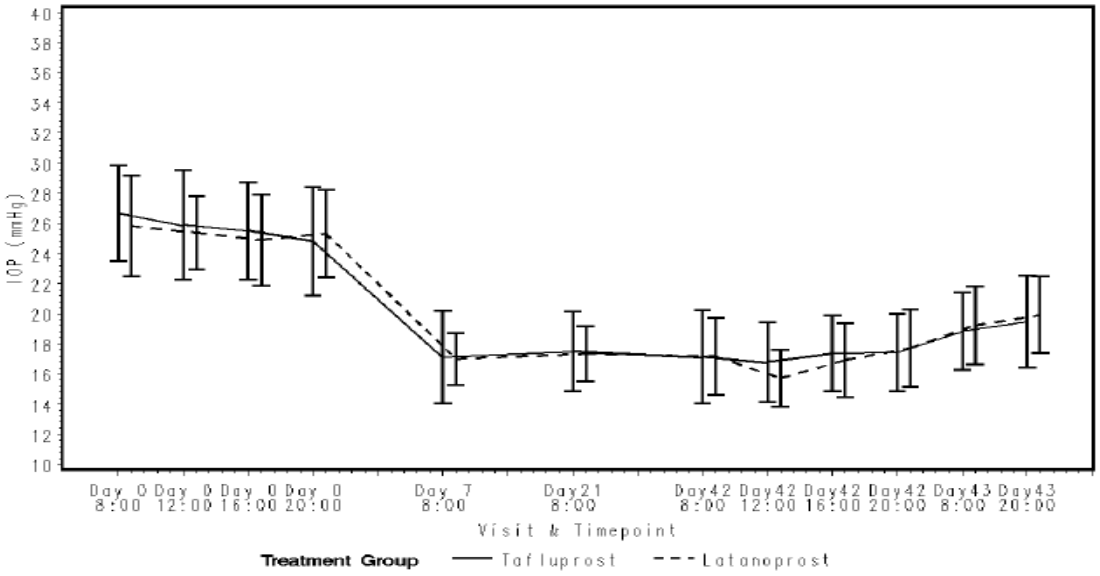


Table 19. Study 74457. Proportion of responders at day 42 (based on decrease in mean diurnal IOP)

	Tafluprost (N=18[1])		Latanoprost (N=18[1])	
Response criteria	No	Yes	No	Yes
≥15% decrease	0 (0.0%)	18 (100.0%)	0 (0.0%)	18 (100.0%)
≥20% decrease	1 (5.6%)	17 (94.4%)	3 (16.7%)	15 (83.3%)
≥25% decrease	5 (27.8%)	13 (72.2%)	4 (22.2%)	14 (77.8%)
≥30% decrease	7 (38.9%)	11 (61.1%)	8 (44.4%)	10 (55.6%)

[1] The two patients (one in both groups) who discontinued due to adverse events at Day 7 were not included in the responder analysis

Study 77552. Open label switch study

An open-label Phase IIIb Study 77552 assessed changes in ocular symptoms and signs as well as conjunctival inflammatory markers when 158 patients with POAG or OHT were switched from preserved latanoprost 0.005% eye drops to tafluprost 0.0015% preservative free eye drops. The mean IOP at baseline was 16.77mmHg and this was maintained after switching to tafluprost; a mean IOP of 16.36mmHg at Week 6 and 16.44mmHg at Week 12. At Week 12, the difference was only marginally statistically significant (p=0.049). While this study predominantly assessed change in symptoms and signs when switching to the preservative free tafluprost formulation, results showed a maintenance of IOP control over 12 weeks of treatment following switch from latanoprost to tafluprost.

Japanese studies

Synopses of the Japanese studies were provided in the current Australian submission. The studies included: Phase II dose-finding Study 850202 (0.0003%, 0.0015%, 0.0025% tafluprost); Phase III latanoprost non inferiority Study 850303; Phase III placebo-controlled Study 850304; Phase III open label 12 months safety Study 850305; and ocular haemodynamics pharmacology Study 850502. Due to the differences in population, design and dosing (morning), these studies did not form part of the current application and were therefore not evaluated.

Evaluators overall conclusions on clinical efficacy

There were two dose-ranging studies in the current Australian submission. The first, Study 15-001, evaluated three doses of tafluprost (0.001%, 0.0025% and 0.005%) together with a placebo and active (latanoprost) control groups. This study found that the greatest

reduction in mean diurnal IOP occurred with the 0.0025% concentration (-5.29mmHg, -22.7%), while both the 0.001% and 0.005% concentrations were slightly less effective (-5.03mmHg, -19.9% and -4.44mmHg, -19.5%, respectively). The data suggested a possible multiphasic dose-effect relationship; the response increases with increasing concentration until reaching a maximal effect at which point further increases in concentration result in a reduced response. As a clear dose-response relationship was not demonstrated, a further dose ranging study was conducted.

In Study 15-002, three tafluprost concentrations were tested (0.0003%, 0.0015%, and 0.0025%) together with two active control groups (timolol and latanoprost). This study found that 0.0015% tafluprost showed the greatest IOP lowering effect. Using a RM ANCOVA it was found that the relative order of effectiveness in reducing IOP (with estimated mean change in IOP) was 0.0025% tafluprost (-5.10mmHg) ≈ 0.0003% tafluprost (-5.17mmHg) < timolol (-5.58mmHg) < 0.0015% tafluprost (-6.46mmHg) < latanoprost (-6.60mmHg). For the 0.0015% dose there were no statistically significant differences with the active controls (latanoprost and timolol). The lowest dose, 0.0003% tafluprost, was significantly inferior to latanoprost and the dose of 0.0015% was statistically superior to 0.0025% tafluprost.

Tafluprost 0.0015% had shown the greatest efficacy in terms of lowering IOP. While efficacy was seen at concentrations as low as 0.0003%, at this level the IOP lowering effect was statistically inferior to latanoprost.

In the pilot Phase II Study 74457, tafluprost 0.0015% was compared to latanoprost 0.005% and found similar treatment effects. After 6 weeks of treatment, the estimated overall treatment difference (tafluprost-latanoprost) was 0.056 mmHg (95% CI: -1.497 to 1.608 mmHg, p=0.942). IOP reduction was maintained until 36 hours post dose which supported once daily dosing.

The Phase III Study 74458 was a non inferiority trial with latanoprost 0.005%. The primary endpoint was the change from baseline in the overall diurnal IOP after 6 months of treatment. From the RM ANCOVA model, using the ITT efficacy dataset, the overall treatment difference was 1.44mmHg with the upper limit of the 95% CI at 1.84mmHg. This exceeded the preset non inferiority limit of 1.5mmHg. Non inferiority was also not reached with the PP efficacy dataset (difference 1.29 mmHg, upper 95% CI 1.69). After 24 months of treatment non inferiority to latanoprost was still not demonstrated on the model adjusting for baseline IOP (ANCOVA) though it was noted on the ANOVA model. From this study it can be concluded that the IOP lowering effect of tafluprost was less than that of latanoprost.

The Phase III pivotal Study 15-003 was a non inferiority trial with timolol. The treatment difference in mean diurnal IOP at 6 months between tafluprost and timolol was -0.28mmHg with the upper limit 95% CI being 0.21mmHg. Non inferiority to timolol was demonstrated in the ITT and PP analysis and also by the criteria set by the FDA which included analysis at each timepoint during the 6 months of the study. IOP lowering effect was maintained over 12 months of treatment and was non-inferior to timolol throughout this period.

The other Phase pivotal III study (74460) assessed the effect of tafluprost as adjunctive treatment to timolol 0.5%. After 6 weeks of treatment, a lowering of IOP was seen in both groups (tafluprost and vehicle) however there was an additional lowering effect with tafluprost of 1.49mmHg which reached statistical superiority (upper limit of the 95% CI being -0.66mmHg, p<0.001). This was confirmed on the PP dataset and the sensitivity analysis. Superiority was found at all timepoints. On switching from vehicle to tafluprost in the extension period, the vehicle subjects reached similar IOP level as the tafluprost group.

As the clinical development program used the preservative containing formulation, a Phase III crossover efficacy study was undertaken (Study 77550). In this trial both the

preserved and unpreserved formulations of tafluprost showed a reduction in IOP from Week 1 of treatment to Week 4 (approximately 5mmHg). Using the pre-specified equivalence range of -1.5mmHg to 1.5mmHg, the formulations were found to be equivalent. From the ITT dataset, the difference in IOP was 0.01mmHg (95% CI: -0.46, 0.49, p=0.96). For the PP efficacy dataset the difference was -0.05 (95%CI: -0.52, 0.42, p=0.83).

The current Australian submission also included Study 77552 which was an open label Phase IIIb study predominantly assessing safety when subjects were switched from preservative containing latanoprost to preservative free tafluprost. The difference from baseline (on latanoprost treatment) in mean IOP value after 12 weeks of treatment was 0.33mmHg (p=0.049) indicating a maintenance of IOP control after change of treatment.

Efficacy for tafluprost has been based on the reduction in IOP which is standard for glaucoma medications. The clinical development program is comprehensive, represented the target patient population and included long term data (240 subjects for 12 months and a further 185 subjects for 24 months). Tafluprost 0.0015% has demonstrated efficacy in reducing IOP, as summarised in Table 20, with a mean reduction in IOP of 6.3mmHg (SD 2.9) from the Phase II and III studies. The efficacy was non-inferior to timolol, though inferior to that seen with latanoprost. Efficacy was demonstrated as adjunctive therapy with timolol, maintained over longer term treatment of 24 months and consistent across subgroups (age, gender, race, disease diagnosis and prior prostaglandin use) (Table 21).

All pivotal trials were conducted with the preservative containing formulation, so it was critical to see that the bridging cross-over study found equivalence in IOP reduction between the formulations.

Table 20

Mean Diurnal IOP Reducing Effect of 0.0015% Tafluprost Ophthalmic Solution at Endpoint (4, 6 or 26 weeks of treatment) in Individual Phase II and Phase III Clinical Trials (except 77552)

Study ID/Phase/ Duration	Specification	Baseline IOP (mmHg)	Endpoint IOP (mmHg)	Change in IOP (mmHg)
WW-15-002-US II (Dose finding study II) 4 weeks	Mean±SD N	23.9±3.5 30	18.1±3.0 29	-6.0±2.6 29
74457 II Pilot latanoprost comparison 6 weeks	Mean±SD N	25.7±3.2 19	17.2±2.5 18	-8.7±2.9 18
74458 III Latanoprost non-inferiority 26 weeks	Mean±SD N	24.3±3.0 263	17.2±2.9 240	-7.0±2.9 239
15-003 III Timolol non-inferiority 26 weeks	Mean±SD N	23.9±3.1 265	18.1±2.9 249	-5.8±2.9 249
74460* III Timolol adjunctive study 6 weeks	Mean±SD N	23.8±2.3 93	18.2±2.9 90	-5.6±2.9 90
77550# III Preserved/unpreserved formulation equivalence 4 weeks per treatment period	Mean±SD N	21.7±2.7 42	16.6±2.0 42	-5.1±2.4 42
All studies II-III	Mean±SD N	23.9±3.0 712	17.7±2.9 668	-6.3±2.9 667

* Only randomized treatment period; adjunctive treatment with timolol #) Only preservative-containing solution.
ITT datasets were used, and mean diurnal IOP was calculated only if all diurnal measurements were available.

Table 21

Mean Diurnal IOP Reducing Effect of 0.0015% Tafluprost Ophthalmic Solution at Endpoint (4, 6 or 26 weeks of treatment) in Subpopulations Based on Pooled Data from Studies WW-15-002-US, 74457, 74458, 15-003, 74460 (only randomized treatment period), and 77550 (only preservative-containing formulation)

Subpopulations	Baseline diurnal IOP (N)	Baseline diurnal IOP (mmHg)	Endpoint diurnal IOP (N)	Endpoint diurnal IOP (mmHg)	Reduction of diurnal IOP (N)	Reduction of diurnal IOP (mmHg)
Gender						
Females	(427)	23.8±2.9	(406)	17.6±2.9	(406)	-6.1±2.9
Males	(285)	24.2±3.1	(262)	17.7±3.0	(261)	-6.4±3.0
Age						
18-40 years	(24)	23.7±3.6	(21)	16.1±2.0	(21)	-6.9±3.0
41-50 years	(78)	24.1±3.0	(72)	18.1±3.2	(72)	-6.0±3.1
51-60 years	(179)	23.9±3.0	(164)	17.4±3.0	(164)	-6.5±2.9
61-70 years	(251)	23.9±3.0	(239)	17.7±2.8	(238)	-6.1±2.7
71-80 years	(154)	24.0±3.0	(146)	17.8±2.9	(146)	-6.2±3.2
>80 years	(26)	24.5±3.2	(26)	17.9±2.7	(26)	-6.7±3.3
Race*						
Caucasian	(598)	24.0±2.9	(562)	17.7±2.9	(561)	-6.4±2.9
Black (incl. East Indian)	(75)	23.9±3.4	(69)	17.5±3.0	(69)	-6.3±3.0
Hispanic	(38)	22.9±2.7	(37)	17.9±2.6	(37)	-4.8±2.6
Disease						
POAG	(432)	24.1±3.0	(408)	17.6±2.9	(407)	-6.5±3.0
Capsular glaucoma	(27)	24.7±3.4	(26)	17.8±2.9	(26)	-6.6±3.4
Pigmentary glaucoma	(7)	25.7±4.0	(7)	17.9±3.3	(7)	-7.8±4.4
Ocular hypertension	(246)	23.6±2.9	(227)	17.8±2.8	(227)	-5.8±2.7
Previous treatment*						
Prior PG users	(372)	23.9±3.2	(344)	17.9±2.9	(344)	-6.0±2.9
PG naive patients	(340)	24.0±2.8	(324)	17.4±2.9	(323)	-6.6±3.0

* One Asian patient was included in ITT dataset of the study 74458, but it was excluded from this table since the patient discontinued the study.

** Based on prior medication data (medications taken 30 days prior to screening) in Phase II studies 74457 and WW-15-002-US.

Study 77552 was not included. ITT datasets were used, and mean diurnal IOP was calculated only if all diurnal measurements were available (Mean±SD).

Safety

Introduction

There are two Phase II and five Phase III trials providing safety data; however pooled safety data is presented from the two Phase II (15-002 and 74457) and four Phase III trials (74458, 15-003, 74460, 77550) for subjects who received at least one dose of tafluprost 0.0015% concentration. All these studies assessed the preservative containing formulation. Safety data on the preservative free formulation comes from the two Phase III trials (77550 and 77552) and due to the open label nature of Study 77552, this data is presented separately. Long term data is derived from two trials: Study 15-003 over 12 months and Study 74458 over 24 months. Japanese Phase II and III studies including 544 tafluprost subjects were not included in the safety discussion due to differences in design, population and administration (morning dosing).

Safety was assessed in the Phase II and III trials by recording adverse events (AE), laboratory evaluations (blood chemistry, haematology, and urinalysis) and vital signs assessment. In addition, specific ocular safety assessments were conducted. The status of the cornea, conjunctiva, iris, lens, vitreous and the retina were investigated routinely by recording visual acuity, visual fields, slit-lamp microscopy and ophthalmoscopy. Conjunctival hyperaemia was assessed by investigators using standard photos as reference. Iris, eyelash and eyelid changes were assessed from photos by an independent, masked assessor. Corneal endothelial cells were assessed using microscopy in selected centres in Study 74458 and 15-003. Aqueous flare was measured in selected centres in Study 74458.

Patient exposure

Tafluprost has been evaluated in 1031 subjects in the USA and Europe in Phase II and III studies and the proposed concentration of 0.0015% has been evaluated in 724 subjects for 722.4 patient years. However, the proposed preservative free formulation has been studied in only 200 of these subjects.

With the proposed 0.0015% tafluprost concentration, there were 206 subjects treated for ≥52 to <78 weeks, 56 for ≥78 to <104 weeks, and 132 for ≥104 weeks. Of the 724 subjects treated with 0.0015% tafluprost, the mean age was 62.6 years (range 21 to 88 and 47% (n=340) aged ≥65 years), 433 (59.9%) were female, 608 (84.1%) Caucasian, 75 (10.4%) black, 438 (60.6%) diagnosed with POAG, 251 (34.7%) with OHT and 27 (3.7%) with capsular glaucoma.

Adverse events

In dose-ranging Study 15-001, the incidence of ocular AEs was 40.0% with 0.001% tafluprost, 50.0% with 0.0025%, and 43.0% with 0.005% compared to 16.7% with placebo and 40.0% with latanoprost. In the second dose ranging study (15-002), there was no major difference in the incidence of ocular AEs between the doses (39.3%, 36.7%, 37.9% for 0.0003%, 0.0015%, and 0.0025% tafluprost respectively, compared to 41.4% for timolol and 32.1% for latanoprost). Conjunctival hyperaemia was the most common AE and increased with increasing concentration of tafluprost (10.7%, 20.0%, 24.1% for 0.0003%, 0.0015%, and 0.0025% tafluprost respectively, compared to 13.8% timolol and 14.3% latanoprost).

Adverse events with an incidence of at least 1% from the four Phase III clinical trials are summarised in Table 22. AEs occurred in 484/724 (66.9%) patients treated with tafluprost in the masked US/EU Phase II/III trials (15002, 74457, 74458, 15003, 74460 and 77550) and ocular AEs in 343/724 (47.4%) subjects. The most common AE in patients treated with 0.0015% tafluprost was ocular/conjunctival hyperaemia, reported in 16.0% of subjects, followed by eye pruritus (7.5%), eye irritation (6.8%), eye pain (5.9%), growth of eye lashes (4.1%), visual field defects (4.1%), dry eye (3.9%) and blurred vision (3.3%). Most ocular AEs (77%) were considered by the investigators to be related to study medication. Headache was the most commonly reported systemic AE at 6.9%, followed by nasopharyngitis (6.6%), cough (4.0%), and hypertension (4.0%).

Table 22.

Number (%) of Patients With Specific Adverse Events
Protocols 15002, 74457, 74458, 15003, 74460 and 77550
(Incidence ≥1.0%)

Adverse Event	Tafluprost 0.0015% (N^T=724) n[‡]	(%)
Patients with one or more adverse events	484	66.9
Patients with no adverse event	240	33.1
Cardiac disorders	**19**	**2.6**
Ear and labyrinth disorders	**9**	**1.2**
Eye disorders	**343**	**47.4**
Asthenopia	7	1.0
Blepharitis	11	1.5
Cataract	18	2.5
Cataract nuclear	8	1.1
Conjunctival haemorrhage	7	1.0
Conjunctival oedema	12	1.7
Conjunctival/ocular hyperemia	116	16.0
Dry eye	28	3.9
Erythema of eyelid	11	1.5
Eye discharge	11	1.5
Eye irritation	49	6.8
Eye pain	43	5.9
Eye pruritus	54	7.5
Eyelash discolouration	20	2.8
Eyelash thickening	9	1.2
Eyelid oedema	12	1.7
Eyelids pruritus	7	1.0
Foreign body sensation in eyes	15	2.1
Growth of eyelashes	30	4.1
Iris hyperpigmentation	7	1.0
Lacrimation increased	16	2.2
Photophobia	12	1.7
Punctate keratitis	8	1.1
Vision blurred	24	3.3
Visual acuity reduced	20	2.8
Visual field defect	30	4.1
Gastrointestinal disorders	**64**	**8.8**
Abdominal pain upper	7	1.0
Diarrhoea	11	1.5
Nausea	12	1.7
Toothache	7	1.0
General disorders and administration site conditions	**43**	**5.9**

Table 22. continued.

Adverse Event	Tafluprost 0.0015% (N†=724) n‡	(%)
Chest pain	8	1.1
Immune system disorders	**11**	**1.5**
Infections and infestations	**131**	**18.1**
Bronchitis	12	1.7
Influenza	24	3.3
Nasopharyngitis	48	6.6
Sinusitis	13	1.8
Urinary tract infection	17	2.3
Injury, poisoning and procedural complications	**42**	**5.8**
Investigations	**33**	**4.6**
Metabolism and nutrition disorders	**28**	**3.9**
Diabetes mellitus	7	1.0
Hypercholesterolaemia	21	2.9
Musculoskeletal and connective tissue disorders	**82**	**11.3**
Arthralgia	17	2.3
Back pain	20	2.8
Osteoarthritis	9	1.2
Pain in extremity	12	1.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**12**	**1.7**
Nervous system disorders	**79**	**10.9**
Dizziness	7	1.0
Headache	50	6.9
Psychiatric disorders	**10**	**1.4**
Depression	7	1.0
Renal and urinary disorders	**14**	**1.9**
Reproductive system and breast disorders	**10**	**1.4**
Respiratory, thoracic and mediastinal disorders	**58**	**8.0**
Cough	29	4.0
Pharyngolaryngeal pain	8	1.1
Skin and subcutaneous tissue disorders	**36**	**5.0**
Surgical and medical procedures	**23**	**3.2**
Vascular disorders	**38**	**5.2**
Hypertension	29	4.0

† N = Number of patients who received tafluprost 0.0015%.
‡ n = Number of patients with the corresponding adverse event.

AEs compared to latanoprost and timolol

The overall incidence of AEs was relatively greater with tafluprost than with latanoprost in Study 74458 (176/269, 65.4% versus 166/264, 62.9%, respectively) after 24 months of treatment. The tafluprost-treated patients reported more eye disorders (46.5% versus 43.9%), in particular conjunctival hyperaemia (9.3% versus 5.7%), eye pain (7.1% versus 2.7%), eye pruritus (3.7% versus 1.1%), growth of eyelashes (6.3% versus 4.2%), blurred vision (2.6% versus 1.1%), and visual field defect (6.7% versus 4.9%). Non-ocular AEs were also more frequent in the tafluprost group (133/269, 49.4% versus 114/264, 43.2%) with no specific AE standing out. Drug related AEs were more frequent with tafluprost (34.6% versus 29.2%), but incidence of SAEs was similar in the tafluprost and latanoprost groups (29/269, 11.0% versus 27/264, 9.8% respectively).

Ocular AEs were noted to continue to occur even after months of treatment, as demonstrated by the rise in cumulative AE incidence at 12 and 24 months. At 6 months, 71/269 (26.4%) tafluprost subjects had 130 ocular AEs, at 12 months the cumulative incidence was 102 (37.9%) subjects with 256 ocular AEs. At 24 months there were a total of 127 (47.2%) subjects with 400 ocular AEs. For latanoprost, the incidence at 6 months was 61/264 (23.1%) with 106 ocular AEs. At 12 months there were 91 (34.5%) subjects with 173 ocular AEs and at 24 months there were 117 (44.3%) subjects with 286 ocular AEs.

The incidence of AEs was also greater in tafluprost-treated than in timolol-treated subjects (Study 15-003) (218/267, 81.6% versus 137/191, 71.7%) after 12 months of treatment. Tafluprost-treated subjects had more eye disorders (50.9% versus 44.0%) including conjunctival hyperaemia (18.0% versus 6.3%), eye pruritus (9.0% versus 2.6%), dry eyes (5.6% versus 3.7%), and foreign body sensation in the eyes (3.7% versus 2.1%). Systemic AEs occurred at a similar incidence overall (30.7% versus 27.7%); however, systemic events that occurred more in tafluprost subjects compared to timolol were headache (13.5% versus 6.8%), nausea (3.7% versus 1.0%), hypercholesterolaemia (7.1% versus 3.7%) and cough (7.9% versus 4.2%).

In Study 74460 involving 185 prostaglandin naïve subjects receiving adjunctive treatment with timolol, there were more AEs (44.8% versus 34.8%) and more ocular AEs (41.7% versus 29.2%) in subjects treated with tafluprost+timolol compared to those treated with vehicle+timolol. The incidence of conjunctival hyperaemia and eye pruritus in the tafluprost+timolol group was 18.8% and 14.6%, respectively, compared to 13.5% and 0% in the vehicle+timolol group. Non-ocular AEs were less frequent in the tafluprost group (7.3% versus 12.4%).

Study 77550: Preserved versus preservative free tafluprost equivalence study

In this cross-over study, AEs were reported in 11/43 (25.6%) of the preservative free group compared to 7/43 (16.7%) of preservative-containing tafluprost group (Table 23). Ocular AEs were more frequent in the preservative free group (20 AEs in 11 subjects, 26%) compared to the preserved formulation group (seven ocular AEs in six subjects, 14%), the most common of which was conjunctival hyperaemia occurring in eight compared to two subjects respectively. Systemic AEs were uncommon (one in the preservative free group and three in the preservative-containing group). Ocular safety was similar between groups.

Table 23.

Ocular AEs by Preferred Term, Causality to Tafluprost and Severity in Study 77550 Based on Patient Count

MedDRA Preferred Term	Preservative-Containing Tafluprost Formulation (n=42)			Preservative-Free Tafluprost Formulation (n=43)		
RELATED TO TAFLUPROST	**Mild**	**Mod.**	**Total**	**Mild**	**Mod.**	**Total**
Ocular/Conjunctival hyperemia	1	1	2(4.8%)	7	1	8(18.6%)
Erythema of eyelid	1	0	1(2.4%)	1	0	1(2.3%)
Eye pruritus	1	0	1(2.4%)	1	0	1(2.3%)
Foreign body sensation in eyes	0	1	1(2.4%)	1	0	1(2.3%)
Anterior chamber cell	0	0	0(0.0%)	1	0	1(2.3%)
Blepharitis	0	0	0(0.0%)	1	0	1(2.3%)
Eye pain	0	0	0(0.0%)	1	0	1(2.3%)
Lacrimation increased	0	0	0(0.0%)	1	0	1(2.3%)
Punctate keratitis	0	0	0(0.0%)	1	0	1(2.3%)
Vision blurred	1	0	1(2.4%)	0	0	0(0.0%)
NOT RELATED TO TAFLUPROST	**Mild**	**Mod.**	**Total**	**Mild**	**Mod.**	**Total**
Asthenopia	0	0	0(0.0%)	1	0	1(2.3%)
Conjunctical haemorrhage	0	0	0(0.0%)	1	0	1(2.3%)
Dry eye	0	0	0(0.0%)	1	0	1(2.3%)
Superficial injury of eye	1	0	1(2.4%)	0	0	0(0.0%)

Related: Causality = Possible, Probable or Certain; Not related: Causality = None or Unlikely
A single AE is counted once for each patient in each period, by maximum severity and strongest causality.

Study 77552: Switch study latanoprost to preservative free tafluprost

In this 12 week study, 158 subjects with ocular symptoms or signs on latanoprost 0.005% were switched to preservative free tafluprost 0.0015%. There were 11 subjects with 18 ocular AEs (7.0%) and 52 non-ocular AEs in 36 subjects (22.8%). There were four SAEs (2.5% of subjects) all of which were non-ocular. There was a reduction in the proportion of subjects with ocular symptoms (irritation, foreign body sensation, tearing, itching, dry eye sensation) after 12 weeks of treatment (Table 24). An overall score (0 to 20) on five ocular symptoms was found to reduce significantly from a mean at baseline of 7.9 to 4.3 at Week 12 ($p<0.001$) with improvement starting by Week 2 of treatment. Ocular signs (tear break up time, corneal fluorescein staining, blepharitis, conjunctival redness and tear secretion) were also found to significantly improve by 12 weeks ($p=0.003$ for tear secretion and $p<0.001$ for other signs) (Table 25). Discomfort on drop instillation was reported to decrease from 60% at baseline to 20% at Week 12.

Table 24. Study 77552

Number (Percentage) of Patients With Abnormal Ocular Symptoms at Baseline, Week 6 and Week 12

Ocular Symptom	Abnormal[1] at baseline (N=158)	Abnormal[1] at 6 weeks (N=156)	Abnormal[1] at 12 weeks (N=155)
Irritation/burning/stinging	89 (56.3%)	48 (30.8%)	44 (28.4%)
Foreign body sensation	78 (49.4%)	45 (28.8%)	42 (27.1%)
Tearing	87 (55.1%)	40 (25.6%)	42 (27.1%)
Itching	74 (46.8%)	40 (25.6%)	41 (26.5%)
Dry eye sensation	102 (64.6%)	55 (35.3%)	61 (39.4%)

[1] At least mild severity grading

Table 25. Study 77552

Number (Percentage) of Patients With Abnormal Ocular Signs at Baseline, Week 6 and Week 12

Ocular Sign (worse eye)	Abnormal[1] at baseline (N=158)	Abnormal[1] at 6 weeks (N=156)	Abnormal[1] at 12 weeks (N=155)
Tear break-up time (fBUT)	150 (94.9%)	120 (76.9%)	111 (71.6%)
Corneal fluorescein staining	129 (81.6%)	82 (52.6%)	63 (40.6%)
Conjunctival fluorescein staining	133 (84.2%)	84 (53.8%)	67 (43.2%)
Blepharitis	95 (60.1%)	66 (42.3%)	63 (40.6%)
Conjunctival redness/hyperemia	133 (84.2%)	108 (69.2%)	93 (60.0%)
Tear secretion/Schirmer test	113 (71.5%)	96 (61.5%)[2]	92 (59.4%)[2]

[1] fBUT < 10 sec; At least grade I corneal staining; At least grade II combined (nasal and temporal) conjunctival staining; At least mild blepharitis; At least mild conjunctival redness; Schirmer test value 10 mm or less.
[2] p=0.014 at 6 weeks and p=0.003 at 12 weeks for tear secretion (from McNemar's test for changes from baseline in proportions). For all other signs at both visits p<0.001.

Results from the Comparison of Ophthalmic Medication for Tolerability (COMTOL) questionnaire[23] found medication preference was reported as tafluprost 50%, latanoprost 10% and neither 40%. The impact of medication side effects on a subject's quality of life (QoL) was found to have not changed in 39.2%, to be better in 51.8% and to be worse in 9.1% of subjects. An improvement on the effect of activity limitations on QoL was found in 32.9% of subjects treated with tafluprost, while 7.2% of patients worsened. These QoL results are suggestive of a favourable effect although results may be due to the open-label, uncontrolled study design.

For the objective conjunctival inflammatory markers, there was a reduction in subjects with abnormal levels (≥40%) of HLA-DR positive epithelial cells from 65.8% at baseline to 45.0% at 6 weeks and 57.2% at 12 weeks. The reduction at Week 6 was statistically significant (p<0.001), but this significant difference was not maintained at Week 12 (p=0.077). There was a significant reduction in subjects with abnormal levels of MUC5AC (mucin gene)-expressing goblet cells from 69.7% at baseline to 51.3% at Week 12 (p=0.002).

Ocular safety

Visual acuity

The best corrected visual acuity was monitored at each visit in all studies using the ETDRS chart and logMAR scores with changes from baseline of at least 0.2 logMAR scores (two lines of letters) considered significant. Over 24 months in Study 74458, three subjects (two tafluprost and one latanoprost patients) had decreased acuity due to cataracts. Overall visual acuity remained stable with no evidence of deterioration.

Visual fields

In tafluprost treated subjects in Study 74458, there were 102 (39.1%) right eyes and 108 (42.5%) left eyes with abnormal visual field findings at screening which reduced to 65 (35.3%) and 68 (37.2%) at 24 months. In tafluprost subjects participating in Study 15-003, there were 75 (28.3%) right eyes and 71 (26.8%) left eyes with abnormal findings at screening which reduced to 45 (19.2%) and 55 (23.5%), respectively, at 12 months. Reduction in visual field abnormalities after treatment was similar for the comparators latanoprost and timolol.

[23] The COMTOL (The Comparison of Ophthalmic Medication for Tolerability) is a 37 item, 13-domain tool with 4 global questions. This tool is specific for ophthalmic medication tolerability.

Flare in the aqueous humour

Breakdown of the blood-aqueous barrier results in flare and cells in the anterior chamber of the eye. Laser flare meter measurements were conducted at selected centres. In Study 74458, 44 tafluprost and 37 latanoprost subjects were examined and the incidence was low and comparable for the average flare value (photon/ms).

Biomicroscopy and ophthalmoscopy

The biomicroscopic examination consisted of evaluation of lids, conjunctiva, cornea, anterior chamber, iris and lens for both eyes. Ophthalmoscopy examined the vitreous, retina, optic nerve and cup/disc ratio. Endothelial cell counts on the cornea were performed at selected centres in Studies 74458 and 15-003. Tafluprost was not found to alter the cell number or shape after 6 months of treatment. After 24 months treatment in Study 74458, biomicroscopy examination found that tafluprost induced chemosis similar to latanoprost, both treatments caused punctate keratitis of the cornea (n=9 and 5 respectively) and cataract was the most frequent finding in the lens. One patient in each treatment groups had new cells in the anterior chamber and anterior chamber flare was detected in two tafluprost subjects.

In the ophthalmoscopic examinations, (vitreous, retina, optic nerve and cup/disc ratio), there were slightly more new findings in the vitreous of latanoprost (n=15) subjects than in tafluprost (n=10) subjects, with most being vitreal opacities or posterior vitreous detachments. There was a similar incidence of new findings in retina (19 tafluprost and 20 latanoprost patients) and in the optic nerve (17 tafluprost and 15 latanoprost patients) with most being related to age related macular degeneration. An increase of at least 0.1 in both the vertical and horizontal cup/disc ratio was seen in 2-6% of patients at 24 months with no clear difference between the treatment groups.

Central corneal thickness was assessed in Study 74458 and after 24 months of treatment there was a small decrease in both treatment groups. The mean change from screening to Month 24 for tafluprost group was -10.7 μm for the right eyes and -8.7 μm for the left eyes, which was more than that found for latanoprost (-6.9 μm for the right eyes and -5.0 μm for the left eyes).

Conjunctival hyperaemia

Conjunctival hyperaemia was assessed by investigators using reference photos and a severity grading scale (0= complete absence of hyperemia, 1=mild, 2=moderate, 3=severe, and 4=very severe hyperaemia) in Studies 15001, 74460, 74458, 15003 and 77552. Evaluation was independent to reporting of the AE. In Study 74460, conjunctival redness increased during treatment, with 18.9% of tafluprost + timolol subjects deteriorating at least one severity score compared to 12.2% of the vehicle + timolol group after 12 weeks of treatment.

In Study 74458, an increase in hyperaemia severity score of least one after 24 months treatment was found in 14.9% of tafluprost and 14.0% of latanoprost patients. After 12 month in Study 15-003, 7.5% patients in the tafluprost and 0.6% patients in the timolol group deteriorated by at least one severity score.

In the open label study (77552), when switching from latanoprost to preservative free tafluprost, an improvement at Week 12 in conjunctival redness was seen in 56.8% of subjects (0.5 grade or better with 45.8% reporting one grade or more improvement), worsening was observed in 6.5% of subjects and no change in 36.8% of subjects.

Iris pigmentation

Iris pigmentation, eyelid pigmentation and eyelashes were assessed in studies 74458, 15003 and 74460 from digital photographs by independent blinded evaluators. Assessment was on prostaglandin naïve subjects (as pigmentary changes may have

already occurred in prior prostaglandin users). In Study 74458, after 24 months of treatment, 26% and 28% of eyes treated with tafluprost and latanoprost respectively had increased iridial pigmentation. Subjects with heterochromic eye colour in particular blue/grey-brown, green-brown and yellow-brown were affected. There were no changes in iridial pigmentation in the timolol group of Study 15-003. In the tafluprost group, change was noted in 22% of eyes at Month 12.

Eyelid pigmentation

Eyelid pigmentation was noted in 5.1% of tafluprost subjects at Month 12 (Study 15-003). None of the timolol treated subjects reported eyelid pigmentation. For prostaglandin-naïve subjects, eyelid pigmentation occurred in 15% tafluprost and 5% latanoprost subjects (Study 74458) after 24 months of treatment.

Eyelash change

Changes in eyelashes (primarily growth) after 12 months treatment occurred in around 60% of the prostaglandin-naïve patients treated with tafluprost (Study 15-003). After 24 months (Study 74458) of treatment in prostaglandin-naïve subjects, eyelash changes were more marked in those treated with tafluprost (59.4% right eyes and 51.6% left eyes) compared to those treated with latanoprost (29.4% right eyes and 30.5% left eyes). Most changes were mild in 42-48% of subjects. However, 12-14% of subjects had moderate changes and this number can be compared to 2-3% of the latanoprost group. Eyelash AEs included eyelash growth (4.1%), discolouration (2.6%) and thickening (1.2%).

Serious adverse events and deaths

In the clinical program with tafluprost (including Japanese studies) there were five deaths, none of which were considered to be related to tafluprost by the investigators.

In the 724 subjects treated with 0.0015% tafluprost, there were 58 (8.0%) serious adverse events (SAEs) (Table 26). In Study 15-003, the incidence to 12 month of Saes was 9.4% of the tafluprost subjects and 7.3% of the timolol subjects. There was one ocular SAE in the tafluprost group (retinal vein occlusion) and two in the timolol group (retinal vein occlusion and macular oedema).

In Study 74458, incidence of SAEs to 12 months was 7.6% and 5.3% in the tafluprost and latanoprost groups, respectively. The incidence of SAEs to 24 months was 11.0% and 9.8%, respectively. There were three ocular SAEs in tafluprost-treated subjects : one cataract with surgery, one increased IOP and one retinal detachment. There was also one cataract diagnosed during the post study period. One latanoprost subject had an ocular SAE of cataract[24].

From other studies, there were two other listed ocular SAEs of macular hole and retinal detachment24.[25]. In addition, 18/351 (5.1%) subjects reported SAEs in the Japanese 12 month open label study (850305). The ocular SAEs in this study included cataracts, reduced visual acuity and macular holes. Overall the incidence of SAEs was slightly higher in the tafluprost-treated patients compared to those treated with latanoprost and timolol.

[24] The sponsor noted that this also included surgery and reconstruction of the conjunctival filtering bleb, also judged as not related to study treatment.
[25] The sponsor noted that these were judged by the investigators as not related to study treatment.

Table 26.

Number (%) of Patients With Specific Serious Adverse Events for Tafluprost 0.0015%
Protocols 15002, 74457, 74458, 15003, 74460 and 77550
(Incidence >0%)

Adverse Event	Tafluprost 0.0015% (N^T=724) n[‡]	(%)
Patients with one or more adverse events	58	8.0
Patients with no adverse event	666	92.0
Cardiac disorders	**5**	**0.7**
Angina unstable	1	0.1
Cardiac failure congestive	1	0.1
Coronary artery disease	4	0.6
Ear and labyrinth disorders	**1**	**0.1**
Vertigo	1	0.1
Endocrine disorders	**1**	**0.1**
Goitre	1	0.1
Eye disorders	**5**	**0.7**
Cataract	2	0.3
Macular hole	1	0.1
Retinal detachment	1	0.1
Retinal vein occlusion	1	0.1
Gastrointestinal disorders	**3**	**0.4**
Abdominal pain	1	0.1
Chronic pancreatitis	1	0.1
Diverticulosis	1	0.1
Gastritis	1	0.1
Intestinal obstruction	1	0.1
General disorders and administration site conditions	**6**	**0.8**
Chest pain	3	0.4
Death	2	0.3
Pyrexia	1	0.1
Hepatobiliary disorders	**2**	**0.3**
Bile duct stone	1	0.1
Cholecystitis	1	0.1
Gallbladder disorder	1	0.1
Infections and infestations	**2**	**0.3**
Gastroenteritis	1	0.1
Gastrointestinal fungal infection	1	0.1
Shigella infection	1	0.1
Injury, poisoning and procedural complications	**6**	**0.8**
Fracture	1	0.1
Heat exhaustion	1	0.1
Joint injury	1	0.1

Table 26. continued.

Adverse Event	Tafluprost 0.0015% (N†=724) n‡	(%)
Patients with one or more adverse events	58	8.0
Patients with no adverse event	666	92.0
Cardiac disorders	**5**	**0.7**
Angina unstable	1	0.1
Cardiac failure congestive	1	0.1
Coronary artery disease	4	0.6
Ear and labyrinth disorders	**1**	**0.1**
Vertigo	1	0.1
Endocrine disorders	**1**	**0.1**
Goitre	1	0.1
Eye disorders	**5**	**0.7**
Cataract	2	0.3
Macular hole	1	0.1
Retinal detachment	1	0.1
Retinal vein occlusion	1	0.1
Gastrointestinal disorders	**3**	**0.4**
Abdominal pain	1	0.1
Chronic pancreatitis	1	0.1
Diverticulosis	1	0.1
Gastritis	1	0.1
Intestinal obstruction	1	0.1
General disorders and administration site conditions	**6**	**0.8**
Chest pain	3	0.4
Death	2	0.3
Pyrexia	1	0.1
Hepatobiliary disorders	**2**	**0.3**
Bile duct stone	1	0.1
Cholecystitis	1	0.1
Gallbladder disorder	1	0.1
Infections and infestations	**2**	**0.3**
Gastroenteritis	1	0.1
Gastrointestinal fungal infection	1	0.1
Shigella infection	1	0.1
Injury, poisoning and procedural complications	**6**	**0.8**
Fracture	1	0.1
Heat exhaustion	1	0.1
Joint injury	1	0.1

Table 26 continued.

Adverse Event	Tafluprost 0.0015% (N†=724) n‡	(%)
Lower limb fracture	2	0.3
Lumbar vertebral fracture	1	0.1
Pelvic fracture	1	0.1
Investigations	**2**	**0.3**
Catheterisation cardiac	1	0.1
Intraocular pressure increased	1	0.1
Musculoskeletal and connective tissue disorders	**7**	**1.0**
Back pain	2	0.3
Intervertebral disc protrusion	1	0.1
Osteoarthritis	4	0.6
Spinal osteoarthritis	1	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6**	**0.8**
Bronchial carcinoma	1	0.1
Metastases to liver	1	0.1
Neoplasm malignant	1	0.1
Ovarian adenoma	1	0.1
Prostate cancer	1	0.1
Renal cell carcinoma stage unspecified	1	0.1
Nervous system disorders	**5**	**0.7**
Cerebrovascular accident	2	0.3
Headache	1	0.1
Loss of consciousness	1	0.1
Syncope	1	0.1
Pregnancy, puerperium and perinatal conditions	**1**	**0.1**
Pregnancy	1	0.1
Renal and urinary disorders	**5**	**0.7**
Haematuria	1	0.1
Incontinence	1	0.1
Renal failure acute	1	0.1
Ureteric stenosis	1	0.1
Urogenital haemorrhage	1	0.1
Reproductive system and breast disorders	**3**	**0.4**
Endometrial hypertrophy	1	0.1
Genital cyst	1	0.1
Vaginal prolapse	1	0.1
Respiratory, thoracic and mediastinal disorders	**5**	**0.7**
Dyspnoea	2	0.3

Table 26 continued.

Adverse Event	Tafluprost 0.0015% (N†=724) n‡	(%)
Epistaxis	1	0.1
Pharyngeal haemorrhage	1	0.1
Pulmonary embolism	1	0.1
Pulmonary fibrosis	1	0.1
Skin and subcutaneous tissue disorders	**1**	**0.1**
Skin cancer	1	0.1
Surgical and medical procedures	**6**	**0.8**
Chemotherapy	1	0.1
Cholecystectomy	1	0.1
Coronary arterial stent insertion	1	0.1
Gallbladder operation	1	0.1
Knee operation	1	0.1
Renal transplant	1	0.1
Vascular disorders	**2**	**0.3**
Hypertension	2	0.3

† N = Number of patients who received tafluprost 0.0015%.
‡ n = Number of patients with the corresponding adverse event.

Laboratory findings and vital signs

Clinical laboratory investigations were carried out in the Phase I studies and the two non inferiority Phase III trials (74558 and 15-003) to 12 months of treatment. Data was available for 6 months for Study 74458 (data at 12 months was not provided in the current Australian submission and there were no laboratory investigations performed in the second 12 months of treatment) and for 12 months for Study 15-003. There were no significant findings or evident trends in serum chemistry or haematology parameters or the urinalysis.

In Study 74458, there was a small decrease in systolic blood pressure in both tafluprost and latanoprost treated subjects at Month 6 (4.4mmHg and 3.3mmHg respectively) and no change in heart rate. The difference between treatment groups in the change from baseline at Month 24 was not statistically significant for systolic blood pressure, diastolic blood pressure and heart rate. In Study 15-003 the blood pressure remained stable in both tafluprost and timolol groups and there was a small decrease in mean heart rate in timolol treated subjects (71.3 reduced to 68.6 beats per minute (bpm) at 6 months and 67.9 bpm at 12months) (Table 27). At 12 months, there was no statistically significant difference between treatment groups in the change from baseline in either systolic or diastolic blood pressure, however the reduction in mean heart rate in the timolol group was significant ($p<0.01$).

Table 27. Blood pressure and heart rate in pivotal phase III trials (74458 and 15-003)

Study 74458	Visit	n	Systolic blood pressure (mmHg) Mean (SD)	Diastolic blood pressure (mmHg) Mean (SD)	Heart rate (bpm) Mean (SD)
Tafluprost	Baseline	268	138.2 (16.4)	81.4 (12.2)	71.1 (10.2)
	Month 6	245[1]	133.8 (17.1)	79.8 (11.4)	70.7 (9.3)
Latanoprost	Baseline	263	136.0 (17.7)	80.3 (11.5)	72.0 (9.8)
	Month 6	251	132.7 (18.1)	79.1 (11.1)	70.0 (9.9)
Study 15003	**Visit**	**n**	**Systolic blood pressure (mmHg) Mean (SD)**	**Diastolic blood pressure (mmHg) Mean (SD)**	**Heart rate (bpm) Mean (SD)**
Tafluprost	Baseline	267[2]	132.4 (17.5)	77.3 (10.5)	71.0 (9.1)
	Month 6	251	132.4 (15.9)	76.2 (10.1)	70.9 (9.4)
Timolol	Baseline	191	132.6 (16.3)	77.6 (9.9)	71.3 (9.4)
	Month 6	172	131.5 (16.3)	75.2 (10.2)	68.6 (8.3)

[1] N=244 for heart rate. [2] N=266 for heart rate. bpm=beats per minute.

Safety in special populations

Analysis by specific populations was not conducted in the safety overview or in the individual clinical study reports. It has been noted that the risk of iridial pigmentation is dependent on eye colour. Asthma and COPD subjects were excluded from trials with timolol though allowed in the latanoprost non inferiority study (74458). There were 18 subjects with asthma treated with 0.0015% tafluprost with no evidence reported of worsening asthma symptoms, though medication was altered in two subjects and there was one newly diagnosed asthmatic.

There was one pregnancy in the clinical program (Study 15-003). The patient was reportedly exposed to tafluprost for about one month during the first trimester. A healthy child was delivered.

Safety related to drug drug interactions and other interactions

No drug-drug interaction studies have been conducted due to the low systemic exposure of tafluprost. Study 74460 assessed tafluprost as adjunctive treatment with timolol. There have been no other adjunctive treatment studies.

Discontinuation due to adverse events

Overall there were 23/724 (3.2%) subjects treated with 0.0015% tafluprost who discontinued the study due to an AE and 14/724 (1.9%) due to an ocular AE, The most common of the latter was eye irritation, eye pain, eye pruritus and conjunctival hyperaemia (Table 28).

Table 28.

Number (%) of Patients With Specific Adverse Events Resulting in Discontinuation
in patients treated with tafluprost 0.0015%
Protocols 15002, 74457, 74458, 15003, 74460 and 77550
(Incidence >0%)

Adverse Event	Tafluprost 0.0015% (N†=724) n‡	(%)
Patients with one or more adverse events	23	3.2
Patients with no adverse event	701	96.8
Ear and labyrinth disorders	**1**	**0.1**
Tinnitus	1	0.1
Vertigo	1	0.1
Eye disorders	**14**	**1.9**
Abnormal sensation in eye	1	0.1
Blepharitis	1	0.1
Conjunctival disorder	1	0.1
Conjunctival/ocular hyperemia	3	0.4
Conjunctivitis allergic	2	0.3
Detachment of retinal pigment epithelium	1	0.1
Eye allergy	1	0.1
Eye irritation	4	0.6
Eye pain	3	0.4
Eye pruritus	3	0.4
Lacrimation increased	1	0.1
Ocular discomfort	1	0.1
Scleritis	1	0.1
Vision blurred	2	0.3
Gastrointestinal disorders	**1**	**0.1**
Intestinal obstruction	1	0.1
Hepatobiliary disorders	**1**	**0.1**
Cholecystitis	1	0.1
Investigations	**1**	**0.1**
Intraocular pressure increased	1	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**0.1**
Metastases to liver	1	0.1
Nervous system disorders	**2**	**0.3**
Headache	2	0.3
Pregnancy, puerperium and perinatal conditions	**1**	**0.1**
Pregnancy	1	0.1
Respiratory, thoracic and mediastinal disorders	**2**	**0.3**
Cough	1	0.1
Pulmonary fibrosis	1	0.1
Skin and subcutaneous tissue disorders	**2**	**0.3**
Dry skin	1	0.1
Hypertrichosis	1	0.1

† N = Number of patients who received tafluprost 0.0015%.
‡ n = Number of patients with the corresponding adverse event.

Over the 24 months of Study 74458, there were more discontinuations due to AEs in the tafluprost group than in the latanoprost group (3.3% versus 1.9%). The rate of

discontinuation due to AEs up to 12 months was lower in subjects treated with tafluprost than with timolol in Study 15-003 (9/267, 3.4% tafluprost and 10/191, 5.2% timolol).

Post marketing experience

There have been two periodic safety update reports (PSUR) since product launch and prior to the submission of the Marketing Application in Australia (30 April 2008 and 30 April 2009). Neither PSUR was provided to the Clinical evaluator for review so the following comments are based only on the sponsor's Summary of Clinical Safety which was submitted with the current Australian submission. However, the following PSURs were submitted subsequently: PSUR (30-Oct-09 to 29-April-10) was included with the Sponsor's pre-ACPM response and PSUR (30-April-10 to 29-April-11) was included as part of the S60 Appeal. There have been 82 spontaneous reports to the marketing authorisation holder to this date, 78% ocular and 17% nervous system disorders. There was one serious event of cataract after 2.5 months of treatment. Most nervous system disorders were reported as headache (Tables 29 and 30). There was no breakdown of information by preservative containing or preservative free formulation.

Table 29.

Tafluprost: Market Introduction (30-Apr-2008) through 29-Apr-2009
Summary Tabulation of Spontaneous Reports received
from Healthcare Providers by SOC*

System Organ Class	Total Number of Reports	% of Total Reports	Total # of Serious Reports	% of Serious Reports
Ear and labyrinth disorders	2	2	0	0
Eye disorders	64	78	1	100
Gastrointestinal disorders	2	2	0	0
General disorders and administration	4	5	0	0
Nervous system disorders	14	17	0	0
Respiratory, thoracic and mediastinal	2	2	0	0
Skin and subcutaneous tissue disorders	3	4	0	0
DISTINCT NUMBER OF REPORTS	82		1	

* A single report may include adverse events in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes can be greater than the total distinct number of reports received. Percentages are the percent of distinct number of reports for events in that System Organ Class.

Table 30

Tafluprost: Market Introduction (30-Apr-2008) through 29-Apr-2009
Eye Disorder SOC Adverse Events

System Organ Class PreferredTerm*	Total Events	Serious Events	Non Serious Events
Eye Disorders			
Asthenopia	1	0	1
Blepharal pigmentation	1	0	1
Blepharitis	4	0	4
Cataract nuclear	1	1	0
Ciliary hyperaemia	1	0	1
Conjunctival hyperaemia	5	0	5
Conjunctivitis	2	0	2
Corneal disorder	3	0	3
Corneal erosion	1	0	1
Erythema of eyelid	6	0	6
Eye irritation	7	0	7
Eye pain	1	0	1
Eye pruritus	2	0	2
Eyelid oedema	5	0	5
Eyelids pruritus	2	0	2
Foreign body sensation in eyes	2	0	2
Keratitis	1	0	1
Meibomianitis	1	0	1
Ocular discomfort	1	0	1
Ocular hyperaemia	23	0	23
Photophobia	2	0	2
Punctate keratitis	2	0	2
Vision blurred	1	0	1
Visual acuity reduced	2	0	2
Total Events for Eye disorders:	**77**	**1**	**76**

* Italics: Listed adverse event in CCDS

Evaluator's overall conclusions on clinical safety

The tafluprost safety data is pooled from two Phase II trials and four Phase III trials in which 724 patients were exposed to the proposed dose concentration of 0.0015% tafluprost for 722.4 patient years. The proposed preservative free formulation was studied in 200 of the 724 patients. Two of the Phase III trials had extension arms to provide long term data and there were 206 subjects treated for ≥52 to <78 weeks, 56 for ≥78 to <104 weeks, and 132 for ≥104 weeks. In the pooled data set, the mean age of patients was 62.6 years, 60% were female, 84% Caucasian, and 61% diagnosed with POAG, 35% with OHT and 4% with capsular glaucoma. The Japanese studies involving 544 tafluprost subjects, were not included due to differences in design, population and administration (morning dosing). Along with AE recording, laboratory investigations and vital sign assessment, the trials included in depth ocular safety assessments.

Adverse events occurred in 67% patients treated with tafluprost 0.0015% and nearly half the tafluprost-treated patients (47%) had an ocular AE. The AE profile was similar to other prostaglandin analogues and included ocular/conjunctival hyperaemia (16% of subjects), eye pruritus (7.5%), eye irritation (6.8%), and eye pain (5.9%), growth of eyelashes (4.1%), visual field defects (4.1%), dry eye (3.9%) and blurred vision (3.3%). Non-ocular AEs were less common and the most frequent were headache (6.9%), cough (4.0%) and

hypertension (4.0%). Tafluprost had no notable effect on blood pressure or heart rate and laboratory findings were unremarkable.

Of the 724 subjects, 8% had an SAE. Ocular SAEs were infrequent (0.8%) and included two cataracts, a retinal vein occlusion, an increased IOP, a retinal detachment and a macular hole. There were five deaths in the entire clinical program for patients treated with tafluprost (including Japanese studies) and none of these were considered to be related to tafluprost by the investigators.

Overall, tafluprost appeared to be well tolerated despite the high incidence of ocular AEs, as the study discontinuation due to an AE and an ocular AE was low (3% and 2% of subjects, respectively). This rate was higher than latanoprost (3% versus 2%) but lower than with timolol (3% versus 5%).

Ocular safety, as assessed through visual acuity, visual fields, aqueous humour flare, biomicroscopy and ophthalmoscopy, was generally acceptable. Treatment did not affect visual acuity and showed some improvement in visual fields which was similar to the comparators. There were small numbers of patients with chemosis, punctuate keratitis, cataracts, vitreal opacities, posterior vitreal detachments and macular degeneration. On ocular safety examination 15% of subjects recorded an increase in conjunctival hyperaemia (of at least one severity score) after 24 months treatment.

In prostaglandin naïve subjects, pigmentation changes in the eye were frequent with iris pigmentation changes in 26% of subjects (similar to latanoprost) after 24 months of treatment and eyelid pigmentation in 15% of subjects (compared to 5% with latanoprost). Eyelash changes (of any severity) were common (50-60%) with moderate severity changes occurring in 12-14% of subjects. This was higher than with latanoprost where any change and moderate severity change was noted in 30% and 2-3%, respectively. There is no mention of the effect this change has on patients, although the AE incidence for eyelash growth was 4.1%.

Over 24 months of treatment, there was a trend for higher AE incidence with tafluprost than latanoprost (65.4% versus 62.9%) as well as for ocular AEs (46.5% versus 43.9%), in particular conjunctival hyperaemia (9.3% versus 5.7%), eye pain (7.1% versus 2.7%), eye pruritus (3.7% versus 1.1%). Worsening of conjunctival hyperaemia (one severity grade or more) was similar (14.9% versus 14%). Non-ocular AEs were also more frequent (49.4% versus 43.2%) while SAEs incidence was similar (11.0% versus 9.8%).

Over 12 months of treatment, 81.6% of tafluprost subjects compared to 71.7% of timolol subjects had one or more AE. Ocular AEs were more frequent with tafluprost (50.9% versus 44.0%), in particular conjunctival hyperaemia (18% versus 6.3%), eye pruritus (9.0% versus 2.6%) and dry eyes (5.6% versus 3.7%) were reported. A worsening of conjunctival hyperaemia on ocular examination was also more pronounced (7.5% versus 0.6%). The overall incidence of non-ocular AEs was slightly greater with tafluprost than with timolol (30.7% versus 27.7%), with more AEs of headache, nausea, cough and hypercholesterolaemia reported. SAEs occurred in 9.4% tafluprost subjects and 7.3% timolol subjects, while discontinuations due to AEs were higher with timolol (5.2%) than tafluprost (3.4%).

The study assessing tafluprost treatment on top of timolol did not have a tafluprost only arm so direct assessment of additive side effects was not possible. However, it is noted that the incidence of eye pruritus was high (-14.6%) for those treated with tafluprost+timolol and greater than reported in other studies with tafluprost alone.

Whilst it may have been expected that the incidence of ocular AEs would be lower with an eye drop without preservative, in Study 77550 the incidence of AEs was higher in the preservative free tafluprost group compared to the preserved formulation group (25.6% versus 16.7%). The incidence of ocular AEs (26% versus 14%) was also higher although

the ocular safety assessments were similar between the groups. There were no SAEs in either group. This cross over study was small (43 subjects) and only of four weeks duration for each arm so it is not possible to draw definitive conclusions on the relative safety of the product. Needless-to-say, it is of concern that the rate of ocular AEs in the proposed formulation for marketing is higher than that seen with the formulation currently marketed on which the majority of safety data is based.

The 12 week study switching 158 subjects with mild ocular symptoms or signs with latanoprost to preservative free tafluprost (Study 77552) found improvements across a number of areas (symptom scores, ocular signs, QoL measures, and drop discomfort). There was improvement in one conjunctival inflammatory marker, however, the other marker (HLA-DR positive epithelial cells) was only significantly improved at 6 weeks and not at 12 weeks. While improvements were seen in subjective assessments, it was not encouraging to see a negative result on the objective inflammatory marker. In addition, the open label design may have introduced bias in assessments as there was no direct comparison arm. For these reasons the clinical evaluator felt that it was not possible to draw definitive conclusions on the relative safety of the preservative free product from this study. In the clinical program there was only one pregnancy reported; a healthy baby was delivered following about four weeks of drug exposure in the first trimester.

The sponsor did not provide any subgroup analysis of the safety data such as by age group, gender, race or in treatment-naïve patients.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated. Below is a list of the clinical evaluator's questions and summaries of the responses provided by the sponsor.

Pharmacokinetics (PK)/Pharmacodynamics (PD)

These questions are equally relevant to both the PK and PD sections of the report:

1. Does hepatic impairment affect the PK/PD of tafluprost?

Sponsor's answer: Due to the very low plasma concentration of tafluprost acid and its rapid elimination from plasma, it is unlikely that hepatic impairment will cause systemic accumulation leading to systemic adverse effects. The sponsor plans to address the limited data in the PI.

2. How are the PK/PDs of tafluprost affected by commonly co administered medication, such as timolol?

Sponsor's answer: Study 74460 evaluated the efficacy and safety of tafluprost 0.0015% eye drops as adjunctive therapy with timolol 0.5% eye drops in 185 patients. Results from this study showed that addition of tafluprost therapy to timolol provided greater lowering of IOP compared to timolol and vehicle. Furthermore, on switching from vehicle to tafluprost in the extension period, the vehicle subjects reached similar IOP levels as the tafluprost group. This study confirmed that there is additive pharmacological effect when tafluprost is used as adjunctive therapy with timolol.

3. Is there a difference in the PK/PD between male and female subjects?

Sponsor's answer: Pharmacokinetics in special populations were not examined as this product is intended for ocular use and to act locally without systemic effects. Pharmacokinetic data were obtained in two Phase I clinical studies (Study 15-005 and

Study 7751) among healthy young adult male and female subjects. Neither study revealed any meaningful difference in drug exposure due to gender.

4. Are there any secondary PD effects related to the use of tafluprost?

Sponsor's answer: Tafluprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular system and no secondary pharmacodynamic effects have been reported with the use of tafluprost. Tafluprost did not produce any ocular or systemic effects in clinical trials beyond those that have been reported for marketed prostaglandin analogues.

Efficacy

5. The feasibility study for paediatric development should be provided.
6. The clinical study report for the 12 month data from Study 74458 were not included in the current Australian submission and should be provided for review.
7. A subgroup analysis should be conducted to examine efficacy in treatment naïve subjects (those who are newly diagnosed or not received any prior medical therapy) as only the prostaglandin naïve patients were examined.

Sponsor's answer: The rationale for limited data in treatment naïve patients is that the treatment effect is expected to be less in patients who are pretreated compared to treatment naïve patients. Therefore, the treatment effect in pretreated patients, which has been included in the current Australian submission, would provide a more conservative estimate of efficacy. A subgroup analysis of efficacy in newly diagnosed patients or treatment naïve patients was included with the sponsor's response. It analysed IOP reduction by prior glaucoma treatment in the four double masked active controlled Phase II and III studies with tafluprost 0.0015% (Studies 15-002, 74457, 74458 and 15-003). The vast majority of point estimates for the treatment difference suggest that there is a strong trend that the relative efficacy of tafluprost compared to timolol and latanoprost is slightly less in patients who have been pre treated compared to treatment naïve patients. However, after all patients have been treated for 6 months and can no longer be considered treatment naïve, this trend becomes less apparent.

Safety

8. Subgroup analyses on the Phase II and III 0.015% tafluprost safety dataset for age (±65 years), gender, race and prior glaucoma treatment, particularly for patients with no prior treatment, should be provided.
9. PSURs should be provided for review. Post marketing information needs to be analysed by formulation type (with preservative or preservative free).

Sponsor's answer: While subgroup analyses were not done in each clinical study, the IOP reducing effect of tafluprost was investigated post-hoc in various subpopulations for the two Phase III pivotal studies (Study 74458 and Study 15-003), individually and combined. Based on sub-group analyses of efficacy data from above mentioned studies, age, gender and race do not appear to affect IOP response in patients who receive tafluprost 0.0015%. Sub-group analyses of IOP reduction by prior glaucoma treatment in the 4 double-masked, active-controlled Phase II and III studies with tafluprost 0.0015% (Studies 15-002, 74457, 74458 and 15-003) showed that the vast majority of the point estimates for the treatment difference suggest that there is a strong trend that the relative efficacy of tafluprost compared to timolol and latanoprost is slightly less in patients who are pre-treated compared to treatment-naïve patients. However, after all patients have been treated for 6 months and can no longer be considered treatment-naïve, this trend becomes less apparent.

Therefore, the treatment effect is expected to be less in patients who are pre-treated compared to treatment-naïve patients. Therefore the treatment effect in pre-treated patients, which is included in the submission, would provide a more conservative estimate of efficacy.

To date the Sponsor has submitted 2 PSURs to the TGA in support of the Marketing Application for tafluprost. PSUR (30-Oct-09 to 29-April-10) was included with the Sponsor's pre-ACPM response and PSUR (30-April-10 to 29-April-11) was included in the S60 Appeal.

Due to the nature of post marketing data collection, it was not possible to separate the data for preservative free tafluprost from preservative containing tafluprost. However, the Sponsor is currently undertaking steps to collect this information. It is anticipated that starting from the second half of 2012, it would be possible to separate safety data for preservative free tafluprost from preservative containing tafluprost, if this information is reported.

Clinical summary and conclusions

Efficacy

The clinical program with tafluprost consisted of two dose ranging Phase II, one pilot Phase II, two pivotal Phase III trials (non inferiority to latanoprost and non inferiority to timolol) and one Phase III study of adjunctive therapy with timolol. The formulation tested in these trials contained preservative (BAK). There were also 2 Phase III trials with the preservative free formulation: a cross-over formulation bridging study and an open label study switching from preservative-containing latanoprost to preservative free tafluprost. A clinical program was also conducted in Japan though it did not form part of this clinical evaluation. All studies have been conducted in accordance with GCP and regulatory requirements.

Patients included in the trials were >18 years of age with open angle glaucoma or ocular hypertension. The main primary analysis for the controlled Phase III studies was the change from baseline in the mean diurnal IOP with the ITT and PP populations using a repeated measurements ANCOVA model. Equivalence was demonstrated if the 95% CI of the treatment difference was within the range of -1.5 and +1.5 mmHg and the non inferiority was demonstrated if the upper limit of the 95% CI was less than 1.5 mmHg. The program included patients with an average age of 63 years, about two thirds female, approximately 60% with POAG, 5% secondary glaucoma and the remainder with OHT. Apart from the greater proportion of women, the patient profile is similar to what is seen in Australia.

Dose ranging Phase II studies assessed doses from 0.0003% up to 0.005% tafluprost. There was a possible multiphasic dose response noted with increasing efficacy (IOP reduction) up to 0.0015% then a reduction in efficacy at higher doses. Efficacy was seen with the lowest dose (0.0003%) although this improvement was statistically inferior to latanoprost. Tafluprost 0.0015% resulted in a mean change in IOP of -6.46mmHg which was not statistically different to 0.005% latanoprost or 0.5%.timolol. The pilot Phase II study found IOP reduction was maintained to 36 hours post dose which supported once daily dosing.

Tafluprost 0.0015% demonstrated consistent efficacy in lowering IOP with a mean change in diurnal IOP of -6.3mmHg (SD ±2.9mmHg) in the six Phase II and III trials (n=667). Efficacy was seen across subgroups (gender, age, race, disease) as well as in prior PG users and PG naïve patients. Efficacy was also maintained during long term treatment up to 24 months. However, efficacy was not evaluated in treatment-naïve patients.

The IOP lowering effect was tafluprost was less than latanoprost 0.005%. Tafluprost did not demonstrate non inferiority (limit set at 1.5mmHg) on either the ITT or PP dataset from the ANCOVA model which adjusted for baseline IOP after 6 months (PP dataset difference 1.29mmHg, upper 95% CI 1.69) or after 24 months of treatment. Tafluprost was found to be non-inferior to 0.5% timolol (twice daily) over 12 months of treatment at all timepoints. In addition, the efficacy of tafluprost was found to be additive with timolol.

Given that the proposed tafluprost formulation for marketing is preservative free, and the clinical program was conducted with the preservative containing formulation, it was critical to find that the two formulations demonstrated equivalent efficacy in reducing IOP after 4 weeks of treatment on both the ITT and PP datasets (Study 77550).[26]. In the open label study (Study 77552), IOP reduction was maintained after patients switched from latanoprost to the preservative free tafluprost formulation.

Safety

Clinical safety data was assessed primarily from 724 subjects exposed to 0.0015% tafluprost in Phase II and III trials for 722.4 patient years. Some 200 of these patients were exposed to the proposed preservative free formulation. There was a moderate size database of longer term treatment with 206 patients treated for 52-78 weeks, 56 for 78-104 weeks, and 132 for 104 weeks or more. The Japanese studies (544 subjects) were not included due to design and population differences. Safety monitoring included detailed ocular examinations.

The incidence of AEs was 67%, with ocular AEs (47%) being the most frequent. The AE profile was similar to that observed with other prostaglandin analogues with the most frequent AEs being ocular/conjunctival hyperaemia, eye pruritus, eye irritation, eye pain, eyelash growth, visual field defects, dry eye and blurred vision. Non-ocular AEs included headache, cough and hypertension. Tafluprost did not have notable effects on blood pressure, heart rate or laboratory examinations. Ocular safety examination, after 24 months treatment, noted an increase in conjunctival hyperaemia (15% of patients), frequent eyelash growth (50-60%), iris pigmentation (26%) and eyelid pigmentation (15%).

SAEs and ocular SAEs occurred in 8% and 0.8% of subjects, respectively. The five ocular SAEs included two cataracts, a retinal vein occlusion, increased IOP and retinal detachment/macular hole.[27],. There were five deaths in the entire clinical program (including Japan) with none attributable to tafluprost.

Compared to latanoprost, tafluprost treatment resulted in slightly higher incidence of non ocular AEs (49.4% versus 43.2%) and ocular AEs (46.5% versus 43.9%), particularly conjunctival hyperaemia, eye pain and eye pruritus. Ocular AEs were also more frequent with tafluprost than with timolol (50.9% versus 44.0%) particularly conjunctival hyperaemia, eye pruritus, and dry eyes. There were also slightly more non-ocular AEs (30.7% versus 27.7%) including headache and nausea. SAE incidence was similar to both comparators. Tafluprost resulted in slightly more AE-related study discontinuations than latanoprost while the frequency was greater with timolol than tafluprost.

Adding tafluprost to timolol did not appear to worsen the AE profile. However, as the study design did not have a tafluprost-only arm, direct assessment was not possible.

The formulation bridging study was small, including only 43 subjects, and was only single (investigator) masked due to differing presentation of the formulations. This made it difficult to draw any definitive conclusions on safety of the preservative-free formulation.

[26] The sponsor commented that this was demonstrated in Study 77550.
[27] The sponsor commented that each of these were judged as not related to tafluprost.

While ocular safety assessments were similar, it was noted that after 4 weeks of treatment, the incidence of ocular AEs was higher with the preservative free formulation compared to the preserved formulation (26% versus 14%).

An open label study assessing subjects with mild eye symptoms and/or signs with preservative containing latanoprost found that preservative free tafluprost gave an improvement across a variety of areas but this did not extend to the objective inflammatory markers. It is not possible to draw conclusions from this trial due to its open label design and lack of comparator arm.

There was one pregnancy in the clinical program; a healthy baby was delivered following one month exposure to tafluprost in the first trimester.

Benefit risk assessment

Benefits

The clinical program was comprehensive with adequate patient numbers and data extending to 24 months duration, although this was for the preservative-containing formulation. Overall, 0.0015% tafluprost was found to be effective in reducing IOP by approximately 6mmHg[28]. This efficacy is maintained over longer term treatment of up to 24 months and extended across subgroups (age, gender, race, disease type, prostaglandin users, and prostaglandin naïve). Tafluprost is able to be given once a day which is important for maximising treatment compliance.

Tafluprost was found to be as effective as the beta-antagonist timolol and its efficacy was additive with timolol as adjunctive therapy. This is important as PG analogues plus timolol is the main treatment combination used in Australia. This comparable efficacy did not, however, extend to latanoprost, where tafluprost failed to demonstrate non inferiority. The choice of prostaglandin analogue is relevant in the Australian setting as latanoprost is the most frequently prescribed PG for glaucoma and generally used as first line treatment.

While the ocular adverse event incidence is considerable close to half of all treated) 46.5% tafluprost (versus 43.9% latanoprost), these AEs appear to be relatively well tolerated as demonstrated through the low trial discontinuation rate due to AEs. Ocular safety was acceptable, with a low risk of ocular SAEs and few findings on thorough ocular safety assessments[29].

The two formulations, preserved and preservative free were found to be equally effective in lowering IOP. Treatment with the preservative free tafluprost formulation appears to show a reduction in ocular symptoms and signs that have resulted from treatment with preservative containing latanoprost, although this data is from an open label and uncontrolled study so could be prone to bias.

As all current marketed glaucoma treatments in Australia contain a preservative, an additional benefit of this treatment could be for patients with allergy or intolerance to the preservative BAK as this is a current unmet medical need.

The single dose container could also potentially decrease the risk of bacterial keratitis that has been associated with multi-dose containers of topical ophthalmic products although this was not assessed clinically in this development program.

[28] Sponsor comment: Overall, 0.0015% tafluprost was found to be effective in reducing IOP by approximately 6 to 8 mmHg in the study comparing tafluprost to latanoprost and 5 to 7mmHg in the study comparing tafluprost to timolol.
[29] The sponsor added the comment that this is comparable to other prostaglandin analogues.

Risks

One of the main risks evident from the clinical evaluation is the significant embryotoxic effects noted in the sponsor's nonclinical overview. This safety risk has also been reported for other ocular PG analogues. Glaucoma is generally a disease of elderly patients, however it is not uncommon for women of child bearing age to suffer for the condition. While there was one pregnancy with a reportedly healthy baby delivered after exposure in the first trimester to tafluprost, there remains an unknown but potential risk to the foetus.

Tafluprost treatment resulted in a significant incidence of ocular adverse events which continued to occur into the second year of treatment, although, as mentioned above, this resulted only infrequently in trial discontinuation. Non-ocular AEs, predominantly headache, were less frequent. The AE profile was consistent with other PG analogues, however the AE incidence was greater than latanoprost and timolol, particularly for conjunctival hyperaemia and eye pruritus.

It is known that treatment with PG analogues can result in pigmentary changes in the iris and eyelid, as well as eyelash growth, and tafluprost was no exception. These changes were tolerated by patients and did not appear to have long term consequences, although the incidence was high and notably greater than in those treated with latanoprost.

There were several areas where data was lacking or limited. There were no studies conducted in patients with hepatic or renal impairment. There appears to be a lack of data on newly diagnosed subjects or those that are treatment naïve as this subgroup was not analysed. There was also no data to provide evidence for the effectiveness of tafluprost as adjunctive treatment with glaucoma medications other than timolol. There was limited data on asthmatics, no information provided for aphakic patients and no data in the paediatric population[30]. There is only limited reliable safety data on the preservative free formulation. This comes from a small sample size, cross-over, single masked and short duration trial. This study found a higher incidence of ocular AEs with the preservative free compared to the preserved formulation[31]. The other safety data on the PF formulation came from an open label, non-controlled trial and so could be biased. As the sponsor is seeking to register only the preservative free formulation in Australia, it is important to know what the incidence would be in a masked, controlled study of adequate sample size[32].

Balance

Open angle glaucoma has been reported as affecting up to 3% of Australian population (Mitchell *et al* 1996[33]). It is a lifelong disease which, whilst not affecting mortality, has significant impact in terms of vision impairment and blindness.

Men and women are equally at risk and this risk increases with increasing age. The mainstay of treatment for glaucoma is reduction in IOP which is accomplished primarily with medical therapy and laser surgery. There is a large array of medical treatments available for IOP reduction including beta-blockers, prostaglandin (PG) analogues, carbonic anhydrase inhibitors, alpha agonists and parasympathomimetics. The PG

[30] The sponsor added the comment that the lack of data in these areas are addressed in the PI
[31] The sponsor added the comment that the small sample size of this study preclude drawing conclusions about the AE profile of preservative free vs. preservative containing tafluprost
[32] The sponsor commented that in addition to the studies included in the original application, further data has been provided from a trial (Protocol 001) using the PF formulation form in a randomised, controlled trial, 12 weeks long, double-masked study conducted with PF tafluprost vs. timolol PF which includes a larger number of patients (643) for a longer duration (12 weeks). Of the 320 patients randomised to tafluprost, 306 completed the study, and of the 323 patients randomised to timolol, 312 completed the study. Both preservative free tafluprost and preservative free timolol were generally well tolerated.
[33] Mitchell P, Smith W *et al* Prevalence of open-angle glaucoma in Australia: The blue mountains eye study. *Ophthalmology*. 1996;103(10):1661-1669.

analogues have gained widespread use as first line therapy for OAG and OHT as they have demonstrated effective IOP reduction, lower systemic side effects and can be given once daily.

There are already three PG analogues used in Australia, latanoprost, bimatoprost and travoprost, with latanoprost being the most frequently used. Second line therapy in Australia tends to be with timolol. Combination therapies, typically latanoprost and timolol in Australia, have become popular due to increased patient compliance. Laser surgery also has a significant place in glaucoma treatment (NHMRC 2009[34]).

The preservative benzalkonium chloride (BAK) has been reported as affecting the tolerability of prostaglandin analogues and contributing to the risk for developing symptoms of dry eyes (Pisella 2002[35], Zabel 1989[36]). In addition, some patients can have a delayed hypersensitivity reaction to BAK (Afzelius 1979[37]). Guidelines commissioned by the National Institute for Health and Clinical Excellence (NICE) state that a preservative free preparation should be offered if there is evidence that the person is allergic to the preservative (NICE 2009[38]) and the European Glaucoma Society states that: "Preservatives contained in topical eye drop preparations may cause inflammatory conjunctival side effects and toxicity of the ocular surface. The use of preservative free preparations may be considered so as to avoid such problems; this can be relevant for certain conditions such as dry eyes or eye with other ocular surface disorders" (EGS 2008[39]).

Currently all available glaucoma ophthalmic drops in Australia contain preservative, therefore a treatment which does not contain BAK provides an important treatment option for this group of patients who are intolerant or hypersensitive to BAK.

Summary of clinical evaluator's report

The sponsor is seeking a broad indication of *reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension*. It was the conclusion of the Clinical Evaluator that this indication is not supported by available data as the efficacy of tafluprost as monotherapy in POAG and OHT was demonstrated in only one of the two pivotal non inferiority trials. The efficacy was comparable to timolol but less than the most frequently used treatment in Australia, latanoprost. In addition, tafluprost treatment also resulted in a higher AE incidence than its comparators. It also caused more eyelid pigmentation and eyelash growth than latanoprost.

The efficacy and safety data support tafluprost use as adjunctive therapy with timolol, so this indication is justified.

There is a current unmet medical need in glaucoma for those with intolerance or hypersensitivity to BAK and, being the first preservative free treatment, there is a clinical need to offer treatment to such patients even if it may be less effective than some other available treatments. The open label study, however, does not include data of sufficient rigor to support this indication and a correctly designed, masked trial would be required.

[34] NHMRC. Systematic literature review on the detection, diagnosis, management and prevention of glaucoma. June 2009
[35] Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol* 2002;86:418-23.
[36] Zabel RW, Mintsioulis G, MacDonald IM, Valberg J, Tuft SJ. Corneal toxic changes after cataract extraction. *Can J Ophthalmo*l 1989;24(7):311-6.
[37] Afzelius H, Thulin H. Allergic reactions to benzalkonium chloride. *Contact Dermatitis* 1979;5(1):60.
[38] National Institute for Health and Clinical Excellence (NICE). Clinical guideline 85. Diagnosis and management of chronic open angle glaucoma and ocular hypertension. April 2009
[39] European Glaucoma Society. Terminology and guidelines for glaucoma. 3rd Edition. 2008.

The sponsor is only seeking to register the preservative free formulation of tafluprost. As the safety database consists predominantly of data on the preserved formulation combined with a signal indicating a possible higher AE incidence with the preservative free formulation, further data is needed to delineate the safety profile of the preservative free formulation. This should be done in a masked and controlled setting to eliminate potential bias.

There are notable areas where data are limited and this must be thoroughly stated in the precaution section of the PI.

Due to the preclinical findings of embryotoxicity, tafluprost should be contraindicated in pregnancy or in women attempting to become pregnant. It should not be used in women of child bearing potential unless there are no other treatment alternatives and adequate contraception should always be in place. As the risk during lactation unknown, treatment during this time should be avoided.

Clinical evaluator's conclusions

The Clinical Evaluator concluded that the overall benefit risk balance of tafluprost is negative for the proposed indication of:

Saflutan is indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension.

The provided data does, however, provide a positive risk benefit balance for the revised indication of:

Saflutan is indicated as adjunctive therapy to beta-blockers in the reduction of intraocular pressure in open angle glaucoma and ocular hypertension.

The indication of the reduction of intraocular pressure in open angle glaucoma and ocular hypertension in patients with intolerance or hypersensitivity to benzalkonium chloride would require positive results from an additional, correctly designed trial addressing this specific indication.

Clinical evaluator's recommended conditions for registration

It is recommended that the condition of approval be subject to the provision of further clinical data on the safety profile of the preservative free formulation. This data should come from a well-conducted, adequately powered clinical trial in which treatment is controlled and masked.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted the Ongoing Safety Concerns and planned pharmacovigilance activities to the Office of Product Review (OPR)as tabulated in Table 31 below.

Table 31. Risk Management Plan

Safety concern	Planned action
Important identified risks:	none
Important potential risks: Embryotoxicity and hyperpigmentation	Routine pharmacovigilance
Important missing information: none	none

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Embryotoxicity	Yes	Tafluprost should not be used during pregnancy unless clearly necessary (in case no other treatment options are available). Tafluprost must not be used in women of childbearing age/potential unless adequate contraceptive measures are in place.
Hyperpigmentation	Yes	No precancerous cases related to hyperpigmentation have been observed. If these cases were appeared, close monitoring would be conducted.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted European Union (EU)-RMP is applicable without modification in Australia unless so qualified:

Pharmacovigilance activities

There is important missing information from the ongoing safety concerns. Children and adolescents below age 18, patients with aphakia, patients with renal and/or hepatic impairment and patients with asthma, patients with neovascular/ angle-closure/ narrow angle/ psuedoexfoliative or congenital glaucoma and patients wearing contact lenses should also be included into the pharmacovigilance plan as 'Important missing

information', while lactating women and possible drug interactions; combination of tafluprost and other prostaglandin analogues should be included under 'Important potential risks'.

The sponsor should conduct postmarketing studies to confirm the safety of the preservative free product and also provide information about the Australian pharmacovigilance unit.

Risk minimisation activities

In support of the Clinical Evaluation conducted by the OMA it is recommended that pregnancy be listed as a contraindication on the PI. The contraindication should also be extended to women attempting to become pregnant. In addition, under 'Interactions with Other drugs' in the PI, a statement should be added that there has been reported paradoxical elevations in IOP when prostaglandin analogues are combined. The sponsor should also detail in the Risk Minimisation Activities section that they have included the above 'Important missing information' and 'Important potential risks' ongoing safety concerns in the Consumer Medicine Information (CMI) and the Precaution section in the PI. The sponsor should also include a warning or notification in the PI and CMI for patients with asthma, or a history of asthma, chronic obstructive lung disease or other breathing problems.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections to registration from a chemistry point of view. The unopened product is to be stored at 2-8^{o}C; the open shelf life is 28 days below 25^{o}C.

All issues raised by PSC have been addressed.

Nonclinical

The evaluator states that adequate studies on pharmacokinetics, dynamics and toxicity were submitted. Topical ocular dosing of tafluprost significantly reduced IOP in normotensive and hypertensive monkeys in a dose-dependent manner. The effect lasted approximately 24 hours; there was an associated increased uveosceral outflow of aqueous humor.

There was a high degree of receptor specificity as seen in secondary pharmacodynamic studies. The studies targeted effects on the CNS, cardiovascular system and respiratory system and also any effects of uterine smooth muscle. There were no consistent effects on general activity, behaviour or locomotion in mice administered IV doses (estimated relative exposure > than 800). There was increased respiratory rate, heart rate, reduced T wave amplitude in dogs (relative exposure 11-80). No ECG abnormalities were seen in monkeys (relative exposure less than 282); transient QTc prolongation was seen in dogs at high exposure margin (approximately 700). Effects on the contractile activity of the isolated rat and rabbit uterus were seen with tafluprost.

Pharmacokinetics: Systemic absorption after topical administration was rapid in both animal species (rats and Cynomolgus monkeys) and humans. Conversion of tafluprost to tafluprost acid was also rapid. Unchanged drug was only infrequently detected. C_{max} and

AUC were dose proportional; there was no accumulation seen. Systemic distribution was much lower than that seen in ocular tissues. Metabolism did not involve CYP to a significant extent. Excretion was also rapid (mainly as metabolites) via urine and faeces.

Tafluprost was well tolerated in single dose toxicity studies in rats (≤ 100 mg/kg PO or 3mg/Kg IV) and in dogs (0.3 µg/kg IV). Higher doses in dogs (3-30 µg/kg IV) provided clinical signs, cardiovascular and respiratory effects.

Repeat dose toxicity studies were conducted in rats (6 months, IV), dogs (9 months, IV) and Cynomolgus monkeys (12 months, topical ocular administration). Rats showed hyperostosis, some effects on bone marrow and effects on haemopoiesis. These were seen at large multiples of exposure. Transient salivation, miosis and increased heart rate were seen in dogs. No systemic side effects were seen in monkeys. In monkeys there was darkening of the iris and discolouration of the lower eyelid. These were associated with increased pigmentation, and darkening of the iris did not reverse in a four week treatment free interval. Effects on the iris occurred at subclinical dose levels (relative exposure, ≥0.7) and on the eyelid mostly at ≥7-times the clinical dose. *In vivo* or *in vitro* studies showed no evidence of genotoxicity. No carcinogenicity was seen in rats and mice.

There was placental transfer of tafluprost and its metabolites in rats. There was also excretion in milk following topical administration. Tafluprost (IV) was teratogenic in rats and rabbits. NOEL for embryofetal effects in rats was approximately 340 times the clinical C_{max} whereas in rabbits it was subclinical (less than 0.75 times). There were still births and death of rat pups. NOEL was not established for these effects. Pregnancy Category D was recommended.

There was no skin sensitisation observed in guinea pigs and no evidence of immunotoxicity in repeat dose toxicity studies.

Overall, there were no nonclinical objections to the registration of Saflutan for the proposed indications.

Clinical

Pharmacokinetics:

The evaluator mentions six clinical studies involving 128 adult (50 were Japanese) subjects. It is stated that many of these studies used a bio-analytical method with low sensitivity "that did not allow the pharmacokinetics of tafluprost or its active metabolite tafluprost acid to be determined". The evaluator has drawn upon nonclinical data, which will not be discussed in this section.

The plasma concentration profile of tafluprost acid generally increased from Day 1 (after the first dose) to Day 8 (following 8 days treatment with 0.0015% tafluprost). The C_{max} on Day 1 was significantly lower than on Day 8 (18.4 pg/mL and 25.2 pg/mL, respectively), as was the $AUC_{0\text{-last}}$ (188.3 ± 128.1 pg.min/mL, 340.2 ± 242.4 pg.min/mL, respectively). A study (W77551) comparing the pharmacokinetics of two formulations (preserved versus preservative free) showed low levels after single dose (Day 1) and repeat dose (Day 8). There were no statistically significant differences seen between the two formulations, however the values had high standard deviations.

Overall the clinical evaluator was critical about the lack of good quality pharmacokinetic data and recommends that the PI include some precautionary statement on the lack of data on special populations especially patients with hepatic impairment.

Eight studies involving healthy subjects and those with increased IOP are discussed in the Pharmacodynamics section above.

There was a reduction in IOP in 16 healthy volunteers using preserved versus unpreserved 0.0015% tafluprost in Study 77551. A study using four strengths (0.0001%, 0.0005%, 0.0025%, 0.005%) once (Day 1) and twice (Day 2) in healthy volunteers showed maximum effect at 12 hours post dose and persisted for the two day treatment period. Statistically significant decreases in IOP (relative to placebo) were seen and a significant effect was noted with the higher concentrations. In a study (WW-74452) comparing two concentrations of tafluprost (0.0025% and 0.0050%) with Xalatan (0.005%) for one week, statistically significant reductions compared to placebo and Xalatan were seen with the higher concentrations on Days 1 and 3 of treatment.

Dose finding: There are two studies discussed in the CER.

Study 15-001 was a double blind randomised placebo controlled multicentre active controlled study in 152 patients with open angle glaucoma on ocular hypertension. Three concentrations of tafluprost (0.001%, 0.0025% and 0.005%) were compared to 0.005% latanoprost and placebo. The proposed dose of 0.0015% tafluprost was not evaluated in this study. Some 152 subjects were enrolled and 93% completed the study. Statistical considerations used in recruiting this number have not been stated. It would appear that the treatment groups included approximately 30 subjects each and would not have been adequate to detect any clinically significant differences.

Baseline characteristics were similar between groups. Some 56% had primary open angle glaucoma (POAG).

On Day 28, mean IOP was lower with tafluprost (0.0025 and 0.005%) compared with placebo. There was a tendency for the 0.001% and 0.0025% formulations to be comparable to latanoprost (0.005%). In this study, 0.0025% produced the greater reduction in IOP, followed by the 0.001% formulation. There was no clear dose response effect noted.

Study 15-002 was a randomised double blind active controlled parallel group study of three doses of tafluprost (0.0003%, 0.0015% and 0.0025%) compared with two active controls (0.5% timolol and 0.005% latanoprost) in 144 patients with POAG or ocular hypertension (OHT). Patients randomised to receive timolol were administered drops twice daily (at 8 am and 10 pm). Those who were randomised to tafluprost or latanoprost received the active treatment in the evening. Again, prestudy statistical considerations were not provided. The treatment group size seems inadequate except to detect large differences.

Approximately 28-30 subjects were randomised to each group and the baseline characteristics were similar between groups. The clinical evaluator mentions that the maximum reduction in IOP effect was noted by Day 14 and the greatest reduction was seen at 8 am. A clear dose response effect was not seen in relation to mean IOP reduction. Responder rates (a 20% reduction at least of IOP) at 28 days showed 0.0015% having the best effect regarding tafluprost. The 8 am levels were better with timolol and latanoprost (but these were not statistically significant).

Efficacy

Pivotal efficacy studies included studies assessing:

Monotherapy versus latanoprost

Study 74458 was a double blind active controlled parallel group Phase III study comparing tafluprost 0.0015% and latanoprost 0.005% eye drops in 553 patients with OAG or OH. This was designed as a non inferiority study up to 6 months. It was continued for 24 months as a double blind study.

After a washout of 4 weeks the subjects were randomised to either treatment. The formulation of tafluprost contained preservative. Patients with open angle glaucoma or ocular hypertension or having untreated IOP of 22-34 mmHg on at least one eye at 8 am at baselines were eligible to enrol. The exclusion criteria were similar to those in other trials of this nature.

The primary efficacy variable was the change from baseline in the overall diurnal IOP at the end of 6 months (IOP in the worse eye). IOP measurements were conducted at 8 am, 12, 4 and 8 pm on scheduled visit days. It also included percentage of responders at 6 months.

Assuming a non inferiority limit of 1.5 mmHg, a standard deviation of 4.5mmHg for the change in IOP and a two-sided Type I error rate of 5%, a sample size of 190 evaluable patients (at least 240 randomised patients) per treatment was required for the study to have a power to 90%. A non inferiority margin of 1.5mmHg was chosen as this is the standard margin used in glaucoma trials. The study was designed as a non inferiority study with the limit set at 1.5 mm Hg.

A total of 533 subjects were randomised (tafluprost=269 and latanoprost =264) and 498 (93.4%) completed 6 months of treatment. Baseline characteristics were similar across the treatment groups. Approximately 75% used antiglaucomatous treatment previously.

The following results were obtained (Table 32). Non inferiority at 6 months was not seen as the upper bound exceeded 1.5.

Table 32. ANCOVA and ANOVA results.

6 Months	RM ANCOVA		RM ANOVA	
Dataset	Difference	Upper 95% CI	Difference	Upper 95% CI
ITT Efficacy RM (N=511)	1.44	1.84	1.08	1.56
PP Efficacy RM (N=467)	1.29	1.69	0.93	1.41
PP sensitivity RM (N=429)	1.13	1.55	0.70	1.20

The proportion of subjects responding to treatment based on a decrease of ≥20% in the mean diurnal IOP, at 6 months was less in the tafluprost group (than the latanoprost group (80.3% versus 89.9%). Other endpoints were generally in line with those reported with the primary endpoint.

The clinical evaluator reported a sustained effect (up to 24 months) which was slightly greater with latanoprost. Proportion responding to treatment was also greater (IOP decrease ≥ 25%: in 65.2% versus 75.4%of subjects, respectively).

Monotherapy versus timolol

Study 15-003 was a 12 month trial where subjects were randomised 3:2 to receive tafluprost 0.0015% once daily or timolol 0.05% twice a day (bid). Inclusion/exclusion criteria were similar to those of Study 74458.

Primary efficacy variable was the change from baseline in the overall diurnal IOP at Month 6. Following FDA discussions, a second primary endpoint was added; IOP at each time point and at each visit through to Month 6. Secondary efficacy endpoints were the same as in Study 74458.

Statistical methods were the same as Study 74458, with the non inferiority limit set at 1.5mmHg but with the addition of primary efficacy analysis including the examination of two-sided 95% CI for the difference in IOP between treatments at each visit to Month 6. Non inferiority to timolol was judged if the upper limit of this CI did not exceed 1.5mmHg at all time points and did not exceed 1.0mmHg at the majority of time points.

Some 458 subjects were randomised; 267 to tafluprost and 191 to timolol). Baseline characteristics were similar between groups. Prior prostaglandin use was approximately 72% in each group. Ocular diagnoses were predominantly POAG (55%) and OHT (43%).

The estimated overall treatment difference (tafluprost – timolol) at 6 months is seen in the Table 33 below.

Table 33. ANCOVA and ANOVA results.

6 Months	RM ANCOVA		RM ANOVA	
Dataset	Difference	Upper 95% CI	Difference	Upper 95% CI
ITT Efficacy RM (N=437)	-0.28	0.21	-0.27	0.29
PP Efficacy RM (N=390)	-0.19	0.30	-0.24	0.32

The additional primary endpoint analysis of comparisons of IOP at all timepoints at each study visit found the upper limit of the 95% CI did not exceed 1.5mmHg at any timepoint. The proportion of responders was similar between groups and other secondary endpoints showed non inferiority.

12 month data: 402 (87.8%) completed 12 months of treatment. The evaluator mentions that the IOP lowering effect was maintained. Tafluprost remained non-inferior to timolol.

Adjunctive therapy with timolol. Study 74460

The randomised, double-masked, placebo-controlled, parallel-group, multinational and multicentre Phase III study (74460) of tafluprost 0.0015% eye drops as adjunctive therapy with timolol 0.5% eye drops in 185 patients with open-angle glaucoma or ocular hypertension who are only partially controlled with timolol treatment. This was designed as a superiority study at the end of a 6 week randomised treatment period. There was a 6 week extension period during which the treatment was administered in an open manner. The tafluprost formulation used in this study contained preservative (BAK). IOP at study entry was to be 22-30 mmHg in at least one eye. Inclusion and exclusion criteria were similar to other studies. However these subjects were all prostaglandin naive.

Primary efficacy variable was the change from baseline in the overall diurnal IOP at 6 weeks (measured at 8 and 10 am and 4 pm). The secondary efficacy variables were: change from baseline in time-wise IOPs at 6 weeks; and at Weeks 2 and 4 and proportion of responders at 6 weeks. In addition, efficacy variables for the extension period were: change from baseline in the overall diurnal IOP at 12 weeks; change from baseline in time-wise IOPs (8 and 10 am and 4 pm) at 12 weeks; and the proportion of responders at 12 weeks.

Some 185 subjects were randomised (96 to timolol+tafluprost and 89 to timolol + vehicle group) and 175 subjects completed 6 weeks and 171 subjects completed a further 6 weeks. Baseline characteristics were similar between groups. The baseline 8 am IOP was 24.56 mmHg ± 2.93 in each group. The length of timolol use before treatment was not stated in the report.

At Week 6, the overall treatment difference (tafluprost-vehicle) was -1.49 mmHg with the upper limit of the 95% CI at -0.66 mm Hg ($p<0.001$) suggesting statistical superiority. At Week 6, there was a 21.9% to 24.0% reduction in the mean IOP in the tafluprost group compared to a 15.9 to 17.5% reduction in the vehicle group-this was at different time points. Once the placebo group received tafluprost for the next six weeks, the magnitude of the changes reduced: the percentage reduction was 26.2%-27.8% in the tafluprost group and 25.9%-26.8% in the vehicle group. This was also seen in the proportion of responders (≥ 15%, ≥ 20% and ≥ 25%). Those with ≥ 30% showed that combination therapy 42.2% was superior (34%).

Therapeutic equivalence of the preservative free formulation versus the preserved formulation: (Study 77550)

This was a randomised investigator masked, multicentre cross over Phase III study that compared the pharmacodynamics of the preservative-containing and preservative free formulations of tafluprost 0.0015% eye drops in 43 patients with open-angle glaucoma or ocular hypertension. These endpoints related to various expressions of IOP reduction. The treatment duration was 4 weeks for each formulation with a 4 week washout in between. The 95% CI for the difference were within preset equivalence range (-1.5 to 1.5 mmHg).

Safety

It was stated in the CER that pooled safety data are presented in two Phase II studies (15-002 and 74457) and four Phase III studies (74458, 15-003, 74460 and 77550) who received at least one dose of tafluprost 0.0015% (n=724). *These were all using preservative containing formulation. The preservative free formulation was used in two Phase III studies, 77550 and 77552. Only 200 subjects were involved.*

The clinical evaluator mentioned that overall incidence of AEs was "slightly greater with tafluprost than latanoprost, especially ocular events". These ocular events continued to occur (cumulative incidence at 12 months and 24 months). More ocular events were reported with tafluprost (Study 15-003) and latanoprost (Study 74458) compared to timolol. Similarly, in the adjunctive study with timolol, there were more ocular events reported with tafluprost+timolol compared with vehicle+timolol.

In Study 77550 (preserved versus preservative free tafluprost equivalence study), ocular events were more frequent 26% versus 14%. However, the numbers in each group (n=43) were small.

There was also a "switch study" of subjects on latanoprost who were switched to preservative free tafluprost submitted. This (Study 77552) was an open label study that assesses changes in ocular symptoms, signs and conjunctival inflammatory markers. Some 158 patients with POAG or OHT were recruited. The clinical evaluator reported ocular symptoms and signs were reduced by Week 12; QoL and objective conjunctival markers also showed improvement with tafluprost. However, due the open uncontrolled design, these findings have limited significance.

The clinical evaluator reported that in prostaglandin naïve subjects, pigmentation changes in the eye were frequent with iris pigmentation changes in 26% of subjects (similar to latanoprost) after 24 months of treatment and eyelid pigmentation in 15% (compared to 5% with latanoprost). Eyelash changes (of any severity) were common (50-60%) with moderate severity changes occurring in 12-14% of subjects. This was higher than with latanoprost where any change and moderate severity change was noted in 30% and 2-3% respectively.

SAEs were infrequent: cataract (n=2), retinal vein occlusion (n=1), increased IOP (n=1) and retinal detachment (n=1).

Overall conclusions of the clinical evaluator

In relation to efficacy it is stated that tafluprost was effective and sustained its efficacy over a 24 month monitoring period. It had comparable efficacy to timolol, however it failed to demonstrate non inferiority to latanoprost (Study 74458) in relation to the specified primary endpoint. Both formulations (preservative and preservative free formulations) were effective. However, the data on the proposed preservative free formulation were limited. The risks discussed are the significant embryotoxic effects and the known local (ocular) effects of prostaglandin analogues. The clinical evaluator also stated that "the AE incidence was greater than latanoprost and timolol, particularly for

conjunctival hyperaemia and eye pruritus". In addition, data are limited on newly diagnosed, treatment naive patients. There are no data on adjunctive treatment other than with timolol.

Due to these limitations, the clinical evaluator recommended a narrower indication:

> *Saflutan is indicated as adjunctive therapy to beta-blockers in the reduction of intraocular pressure in open angle glaucoma and ocular hypertension.*

The clinical evaluator stated that clinical data are required to support the use of tafluprost in patients with intolerance or hypersensitivity to benzalkonium chloride.

Risk management plan

The OPR provided recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted European Union RMP is applicable without modification in Australia unless so qualified (detailed above *under V. Pharmacovigilance Findings*).

Risk-benefit analysis

Delegate considerations

The Delegate's issues and proposed action:

> The clinical evaluator's comments are valid in relation to efficacy. However, in relation to first line therapy, the Delegate was of the opinion that efficacy versus timolol (0.5%) has been shown in one study whilst non inferiority versus latanoprost has not been shown in relation to the primary endpoint in Study 74458, at six months, the sponsor has shown that the magnitude of efficacy was "in line with other prostaglandins". Provided the study findings are included in the clinical trials section, the efficacy data appear to be adequate to approve Saflutan for the reduction of elevated intraocular pressure in OAG or OHT as first line treatment.
>
> In relation to adjunctive therapy, the approval that can be based on the data submitted is, as adjunctive therapy to beta blockers.
>
> With respect to patients who would benefit from preservative free eye drops, the Delegate agreed with the evaluator that additional clinical data are required in this subgroup. The Delegate could not support this indication.
>
> The Committee's advice is sought.

Summary of the response from sponsor

The sponsor made a detailed response to the clinical evaluation report. Of note, the response relating to efficacy, safety (and the risk benefit ratio) and the use of the proposed formulation are discussed below. MSD believes that the benefit/risk remains positive and reviewed key aspects of each side of this ratio, and concluded with a discussion of how preservative free Saflutan fulfils a key unmet medical need.

Efficacy

The sponsor disagrees with the statement made by the clinical evaluator in relation to Study 74458 that: "IOP lowering effect was greater with latanoprost and the primary endpoint was not met at any timepoint through to 24 months".

The following table is submitted to show the differences in IOP between the treatment groups at the above mentioned time points.

Table 34. The estimated treatment differences (tafluprost-latanoprost) during the Study 74458.

ITT Efficacy	RM ANCOVA		RM ANOVA	
Visit	Difference	Upper 95% CI	Difference	Upper 95% CI
Month 3	1.05	**1.46***	0.79	**1.28***
Month 6	1.32	1.73	1.05	1.54
Month 12	1.44	1.86	1.2	1.7
Month 18	1.05	**1.49***	0.81	**1.33***
Month 24	1.15	1.6	0.91	**1.44***
Overall	**1.2**	**1.52**	**0.95**	**1.38***

* Does not exceed the predefined non-inferiority limit (i.e., non-inferiority demonstrated)

In response to the statement by the clinical evaluator that "IOP reduction of 20-30% is clinically relevant and at this level there were notably fewer responders with tafluprost than latanoprost", the sponsor acknowledges this, however states that the reduction observed with tafluprost is in line with that observed with other prostaglandin analogues.

Safety

In relation to the clinical evaluator's comment that "the safety profile of tafluprost was slightly worse than its comparators, latanoprost and timolol", the sponsor has provided a post hoc analysis using Fisher's exact test to compare differences between groups regarding adverse events reported by ≥ 1.0% of the patients.

Eye pain, which was statistically significantly higher in the tafluprost group, was generally attributed to the preservative; in the switch study (Study 77552), local symptoms were reduced in the group administered the proposed formulation (which is preservative free). Renal and urinary disorders were also reported at a higher incidence. The sponsor states that it is unlikely to be due to a treatment effect as systemic bioavailability is low.

Use of the preservative free formulation in the studies: The sponsor maintains that the switch study shows equivalence of the two formulations in relation to efficacy. In addition, the BAK preservative free formulation "would offer a significant benefit and fulfil this unmet medical need".

Overall, the sponsor maintains that the efficacy and safety are comparable to other prostaglandin analogues and requests that the indication be:

> *Saflutan is indicated for the reduction of elevated intraocular pressure in open angle glaucoma or ocular hypertension.*

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, proposed the following recommendation:

ACPM recommended rejection of the submission from Merck Sharp & Dohme (Australia) Pty Ltd to register the new chemical entity tafluprost (Saflutan) eye drops 15 µg per mL.

In making this recommendation, the ACPM advised that there was inconclusive efficacy and inadequate safety data for this product in the submitted studies. Efficacy against the

active comparator, latanoprost, was not established in the pivotal study and in addition, there was a trend for a worse adverse event profile compared to latanoprost.

The ACPM also advised that there was unproven equivalence of the preserved versus the unpreserved product and recommended longer term studies with the formulation proposed for marketing given that this product was likely to be used for as long as 20 - 30 years. Moreover, the notional safety advantages of the unpreserved formulation had not been supported by data.

Initial outcome

Based on a review of quality, safety and efficacy, TGA initially rejected the registration of Saflutan (tafluprost) 15 micrograms per mL preservative free eye drops for the reduction of elevated intraocular pressure in open angle glaucoma or ocular hypertension.

The sponsor applied for a review of this decision under section 60 of the *Therapeutic Goods Act 1989* (the Act). As the review of the initial decision was not completed within 60 days, the initial decision was taken to be confirmed on 27 September 2011 in accordance with subsection 60(4) of the Act. The sponsor then applied to the Administrative Appeals Tribunal for a review of the decision not to register Saflutan.

Final outcome

Under section 42C of the *Administrative Appeals Tribunal Act 1975*, where the parties in a matter before the Administrative Appeals Tribunal reach an agreement about the matter, the Tribunal, if it considers it appropriate to do so, may make a decision in accordance with such an agreement. The TGA and the sponsor reached an agreement about the registration of Saflutan with regard to additional information to be included in the product information and the Administrative Appeals Tribunal made a decision in accordance with this agreement. On 16 December 2011 the Tribunal set aside the decision not to register Saflutan and substituted a decision to approve the registration of Saflutan under subsection 25(1) of the Therapeutic Goods Act 1989 for the following indications:

> *Saflutan is indicated for the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension, as monotherapy or as adjunctive therapy to beta blockers.*

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au