Status of Clinical Development

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R&D Vision and Strategy

- **R&D Vision**

  To produce a continuous supply of drugs and services which address unmet medical needs and contribute to enhancing the patients' QOL.

- **Strategy for Achieving the R&D Vision**

1. Stay up-to-date on trends in unmet medical needs and competitors' R&D activities, in order to concentrate resources on projects which emphasize Santen's strength and lead to achievements.

2. Concentrate resources on the prescription ophthalmics R&D (original and in-licensed), in order to continuously enhance product pipeline and pursue and propose therapeutic advantages of Santen's products and services.

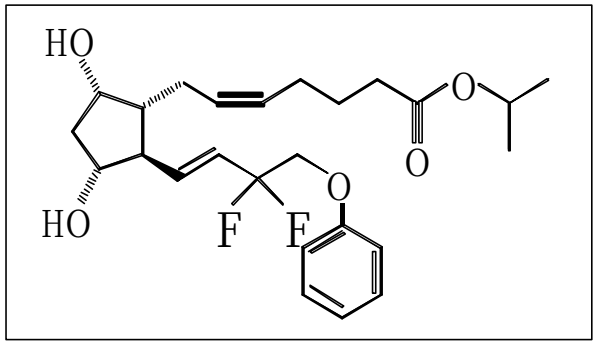
3. For RA/OA, basic plan is to co-develop (in Japan) and out-license (overseas) the new drug candidates that Santen discovered utilizing its original drug discovery approach. Efficient strategies will be devised and executed for co-development projects, including use of public funds.

4. Increase competitiveness by accelerating R&D timelines.

Product Pipeline: Glaucoma Treatment

Generic name (Development code)	Indication	Category/Mechanism	Original/licensor	Stage
Tafluprost (DE-085)	Glaucoma and ocular hyper-tension	Prostanoid FP-receptor agonist. Promotes uveoscleral outflow	Original (co-development with Asahi Glass)	Japan: P3 US/Europe: P3
Olmesartan (DE-092)	Glaucoma and ocular hyper-tension	Angiotensin II AT1 receptor antagonist. Promotes uveoscleral outflow	In-licensed (Sankyo)	Japan: P2 US/Europe: preparing for P2
Lomerizine hydrochloride (DE-090)	Glaucoma	Calcium channel blocker. Improves ocular blood-flow circulation	In-icensed (Nippon Organon)	Japan: P2

DE-085



Generic name:	tafluprost
Indication:	Glaucoma, ocular hypertension
Planned launch:	2007-2008
	(Currently under P3 clinical trials)
Developer：	Co-development, Asahi Glass and Santen
Category:	Prostanoid FP receptor agonist
Mechanism:	Promotes uveoscleral outflow by activating FP receptor
Characteristics:	Potent intra-ocular pressure (IOP)-lowering effect, may have additional value of lowering IOP in normal tension glaucoma patients; aqueous ophthalmic solution with few side effects, which can be stored at room temperature

DE-085: Affinity to Human Prostanoid FP Receptor

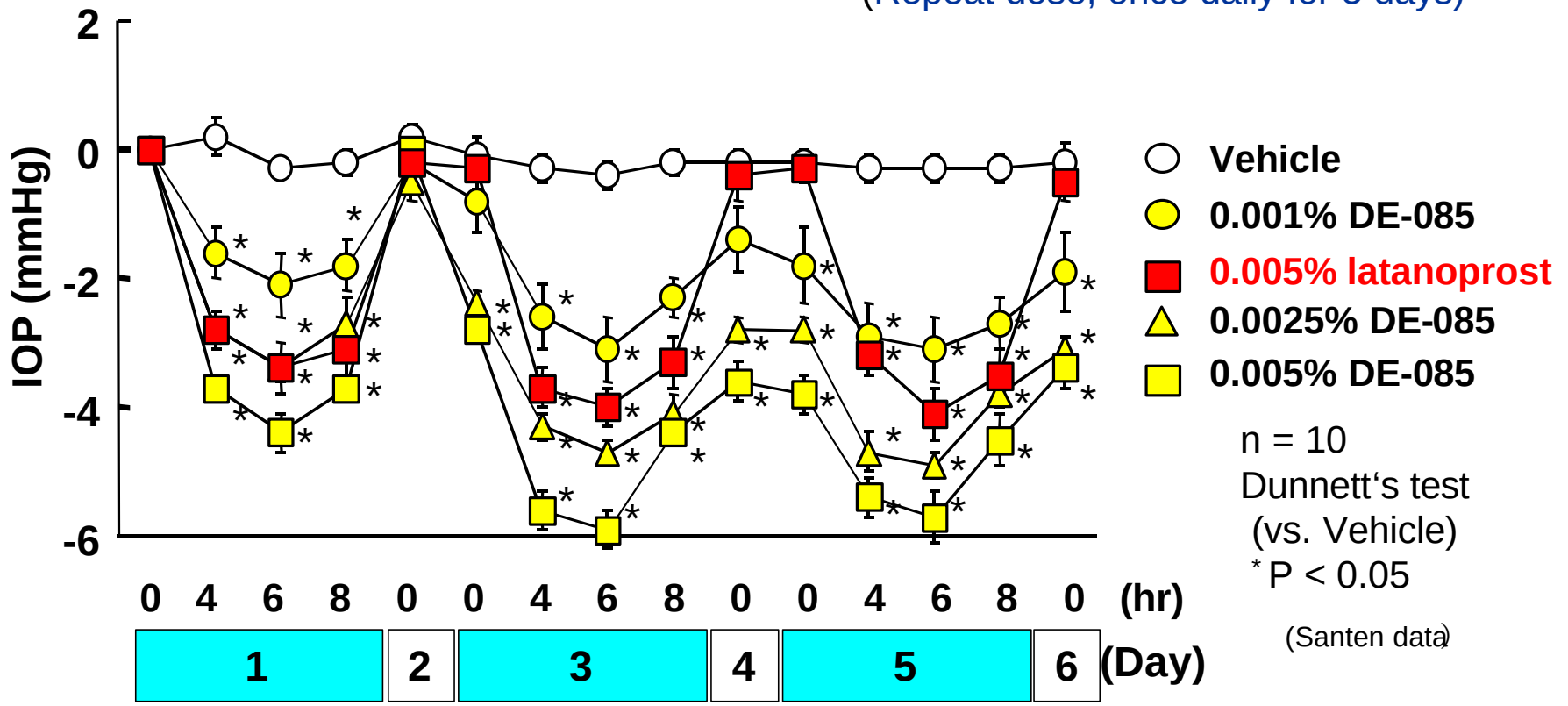
Compound (de-etherized)	K_i (nM)	Ratio (DE-085=1)
DE-085	0.40	1
latanoprost	4.7	12

(Santen data)

DE-085 showed higher affinity to prostanoid FP receptor compared to latanoprost.

DE-085
– IOP Lowering Effect in Non-clinical Studies (Normal IOP Model)

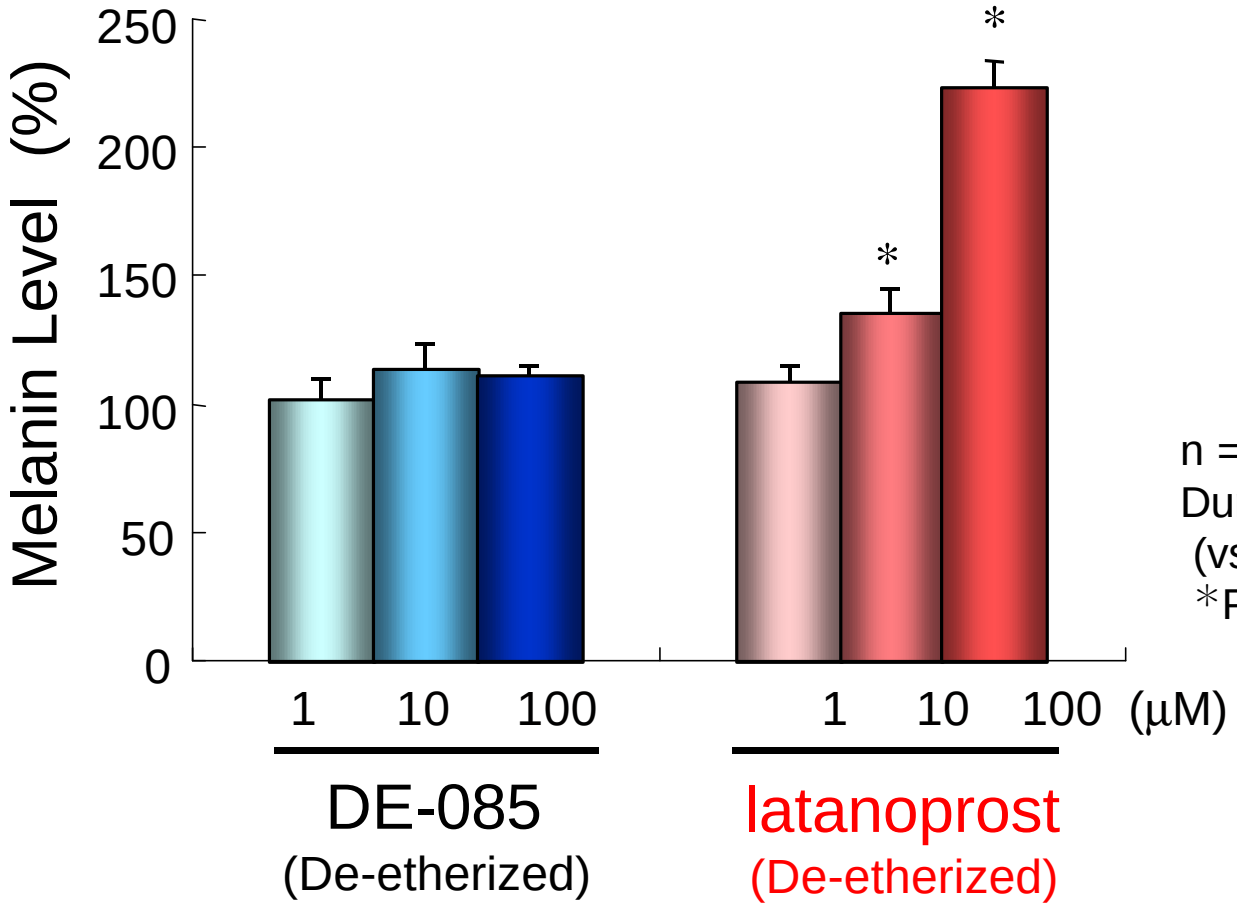
(Repeat dose, once daily for 5 days)



- **DE-085 progressively reduced IOP in concentration-dependent manner**
- **IOP-lowering effect of DE-085 was elevated up to Day 3 and then stabilized**
- **DE-085 significantly reduced IOP even in trough area in which latanoprost does not show any action**

DE-085 – Melanogenesis Promotion *in vitro*

(Cultured B16 melanoma cells,
compound treated for 96 hrs.)



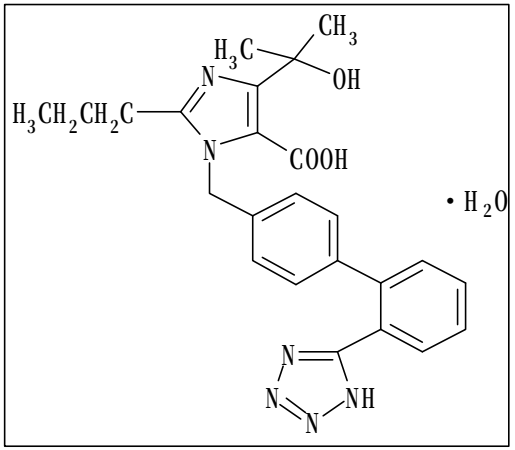
n = 8
Dunnett's test
(vs. Vehicle)
*P < 0.05

(Santen data)

DE-085 did not show melanogenesis promoting effect as was seen in latanoprost

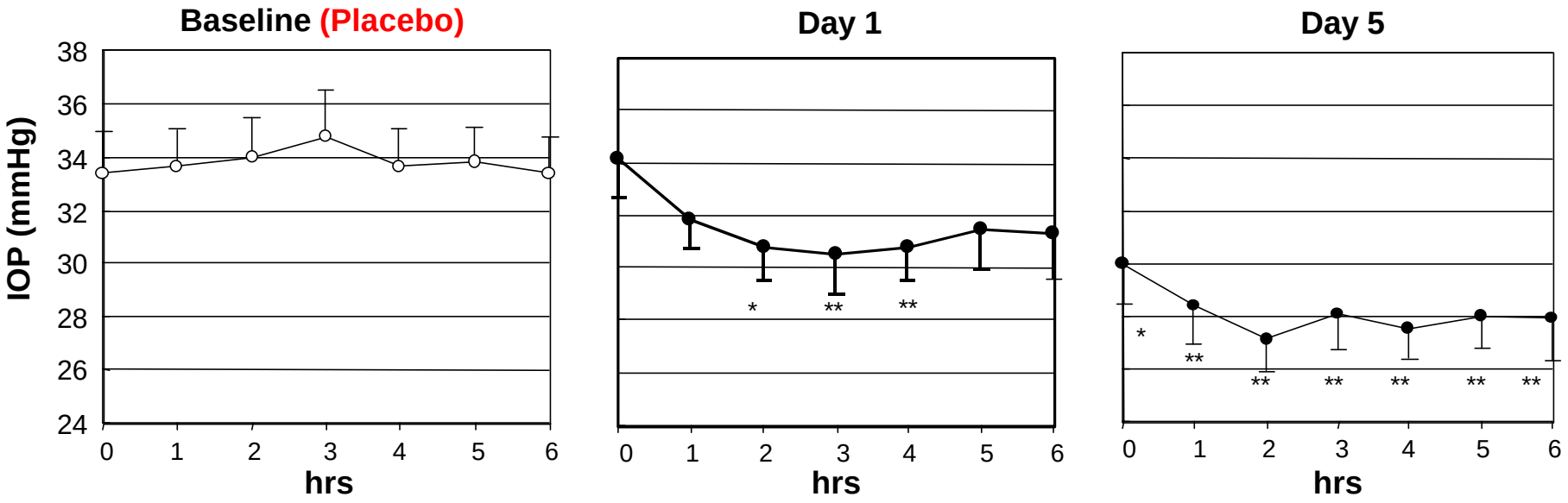
DE-092

Generic name:	olmesartan
Indication:	Glaucoma, ocular hypertension
Planned launch:	2007-2008
	(Currently under P2 clinical trials)
Licensor:	Sankyo
Category:	Angiotensin II AT_1 receptor antagonist
Mechanism:	Promotes uveoscleral outflow of aqueous humor by AT_1receptor antagonizing action
Characteristics:	Totally new mechanism of action. IOP-lowering effect equivalent to beta-blockers and PGs with less adverse effects. Also expected to improve the ocular blood-flow circulation.



DE-092
– IOP-lowering effect in Non-clinical Studies (High IOP Model)

(4% DE-092 ophthalmic solution, repeat dose, twice daily for 5 days)



Mean±S.E.
*p<0.05, **p<0.01,
Compared to placebo at same hour (paired t-test)
(Santen data)

DE-092 showed significant IOP-lowering effect in high IOP model

Product Pipeline: Anti-inflammatory, Cornea and Anti-infective

Generic name (Development code / brand name)	Indication	Category/Mechanism	Original/ Licensor	Stage
levofloxacin 1.5% (IQUIX)	Bacterial corneal ulcer	DNA gyrase inhibitor. Anti-intefcive action.	In-licensed (Daiichi)	US: approved
ciclosporin (DE-076)	Vernal kerato-conjunctivitis	Calicyneurin inhibitor. Immunosuppressant	In-licensed (Novartis)	Japan: NDA
levofloxacin + prednisolone (DE-094)	Infectious keratitis	Fluoroquinolone + steroid. Anti-infective + anti-inflammatory action.	In-licensed (Daiichi)	US: P2
diquafosol tetrasodium (DE-089)	Dry eye	$P2Y_2$ receptor agonist. Stimulates tear secretion.	In-licensed (Inspire)	Japan: P2
sodium hyaluronate (HYALEIN)	Dry eye	Biopolymer cytoprotective agent. Retain water and promotes corneal wound healing.	Original	US: preparing for P2 (Japan: launched)
gefarnate (DE-099)	Corneal & conjunctival epithelial disorder associated with dry eye, etc.	Muco-membranous protective agent. Stimulates mucin secretion.	Original	Japan: preparing for clinical trials

Product Pipeline: Bones and Joints

Generic name (Development code / brand name)	Indication	Category/Mechanism	Original/ Licensor	Stage
Undetermined (DE-096)	Rheumatoid Arthritis (RA)	TNF-alpha inhibitor Inhibit the production of TNF-alpha	Original	Japan: P1
Undetermined (DE-098)	Rheumatoid Arthritis (RA)	Anti-APO-1 antibody. Induces apoptosis in synovial cells	In-licensed (Centocor)	Japan: preparing for clinical trials
bucillaime (Rimatil)	Osteoarthritis	DMOAD. Protects cartilage and modifies edema.	Original	Japan: preparing for clinical trials

Product Pipeline – Changes from Nov. 2003

Generic name (Development code / brand name)	Indication	Region	Stage
levofloxacin 1.5% (IQUIX)	Bacterial corneal ulcer	US	NDA → approved
tafluprost (DE-085)	Glaucoma and ocular hypertension	Japan US/Europe	P2 → P3
olmesartan (DE-092)	Glaucoma, ocular hypertension	US/Europe	Preparing for P2
gefarnate (DE-099)	Corneal & conjunctival epithelial disorder associated with dry eye, etc.	Japan	Preparing for clinical trials