ASP8302
NON-CONFIDENTIAL SUMMARY

astellas

DISCLAIMER

This material includes forward-looking statements based on assumptions and beliefs in light of information currently available to the Astellas and subject to significant risks and uncertainties.

This material contains information on pharmaceuticals (including compounds in research or under development) and other matters. Notwithstanding the foregoing, Astellas makes no representations, warranties, assurances or guarantees of any kind or nature whatsoever, whether expressed or implied, regarding the information in the materials (including, without limitation, no representations, warranties, assurances or guarantees as to the accuracy, sufficiency or completeness of any information, as to whether Astellas has rights to any such information or pharmaceuticals/compounds, as to whether any third party has or does not have any rights to any of such information or pharmaceuticals/compounds, as to the safety, efficacy, or effectiveness of any preparations described in this material, as to the regulatory status of or potential for regulatory agency action regarding any pharmaceuticals/ compounds described in this material, or as to any uses, including unapproved uses, of any such preparations in any fashion). This material does not provide medical advice of any kind.

Astellas undertakes no obligation or duty to change, remove, add, clarify, correct or update any information in the materials at any time.

ASP8302 OVERVIEW

Items	Note
Product name	ASP8302
Mechanism of Action	Positive Allosteric Modulation of Muscarinic M_3 Receptor
Formulation	Small molecule
Target Indication at Astellas	Underactive bladder (UAB)
Development Territory	Europe, Japan
Latest development phase	Phase 2a for UAB

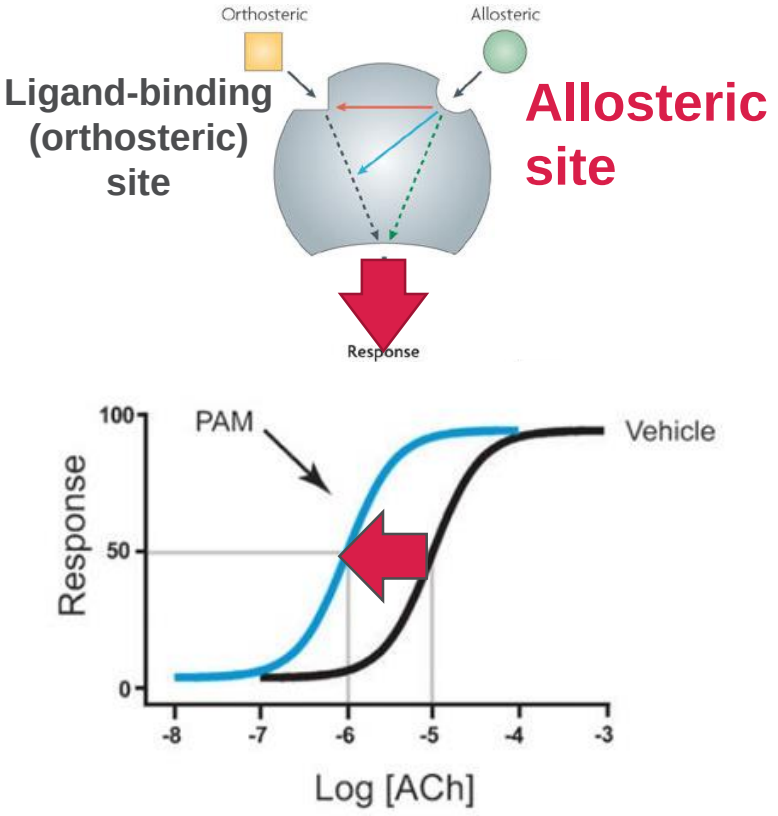
ASP8302 IS A NOVEL POSITIVE ALLOSTERIC MODULATOR (PAM) OF MUSCARINIC M3 RECEPTORS

- **Positive allosteric modulator (PAM) binds to the allosteric site of the receptor and enhances the effect of agonist (acetylcholine, Ach)**

- **PAM is more advantageous than agonists in avoiding side effects**

✓ **Better subtype selectivity**

✓ **No direct receprot activation by itself; enhances the effect of ACh only when ACh is released**



(Conn et al., 2009; Digby et al., 2010)

POTENTIAL INDICATIONS FOR THE M3 PAM ASP8302

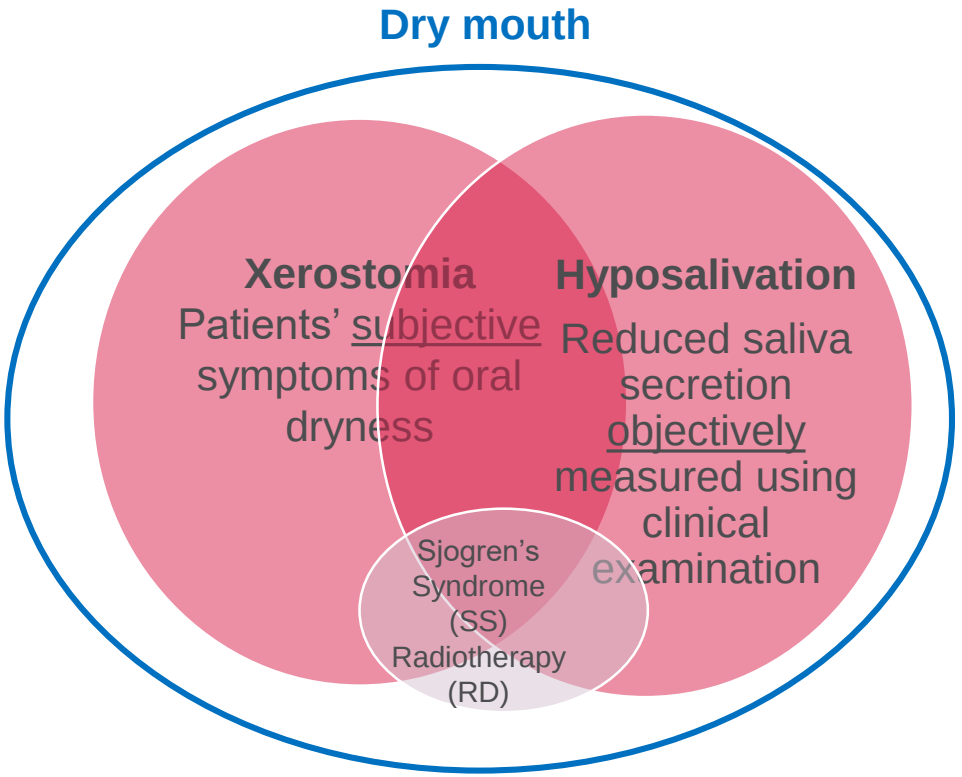
Organ and parasympathetic function mediated by M_3 receptor activation	Indications muscarinic drugs are approved or developed
Bladder: contracts the detrusor muscle	**Bladder underactivity, urinary retention (bethanechol, distigmine)**
Salivary gland: stimulates flow of saliva	**Dry mouth (pilocarpine, cevimeline)**
Gastrointestinal tract: stimulates contractions and peristalses	Ileus (bethanechol, neostigmine, physostigmine), functional dyspepsia (acotiamide)
Eye: constricts pupil, contracts ciliary muscle	Glaucoma, esotropia, miosis, dry eye, presbyopia (pilocarpine, carbachol, aceclidine)

astellas

Icons used under license from Shutterstock.com

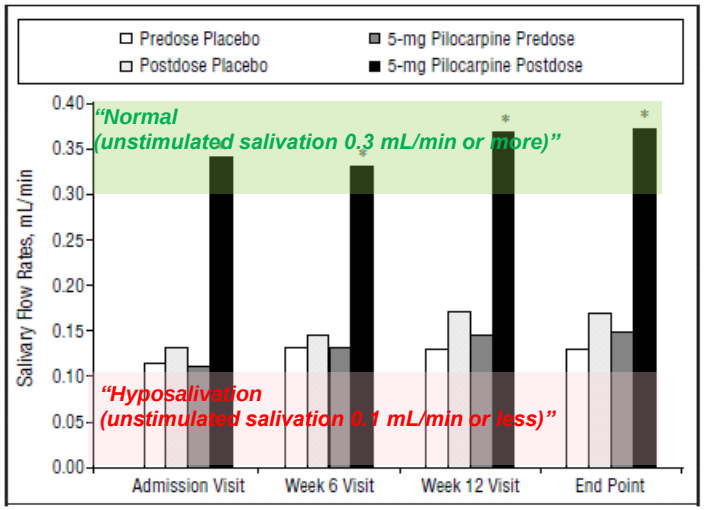
DRY MOUTH: DEFINITION, PREVALENCE, ETIOLOGY, AND DIAGNOSIS

- **A condition including xerostomia and hyposalivation**
- **Highly prevalent: 20 to 30% of general (elderly) population**
  - ✓ See back-up slides for population-based studies
- **Various etiologies, often multifactorial**
  - ✓ Sjogren's syndrome (SS), radiation therapy(RD), drug side effects, stress, infections, dehydration, mouth breathing, etc.
- **Causes various complications and impacts QoL**
- **Muscarinic agonists indicated only for dry mouth caused by SS and RD**

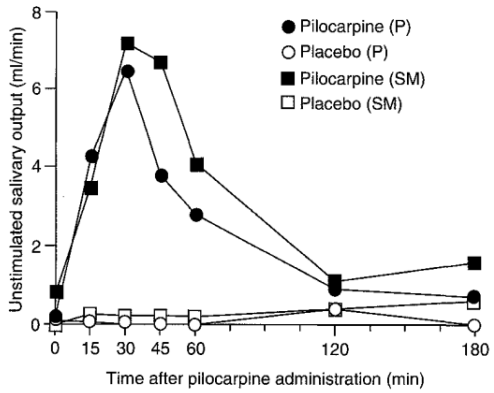


MUSCARINIC AGONISTS TRANSIENTLY ENHANCE SALIVATION WITH HIGH % OF CHOLINERGIC SIDE EFFECTS

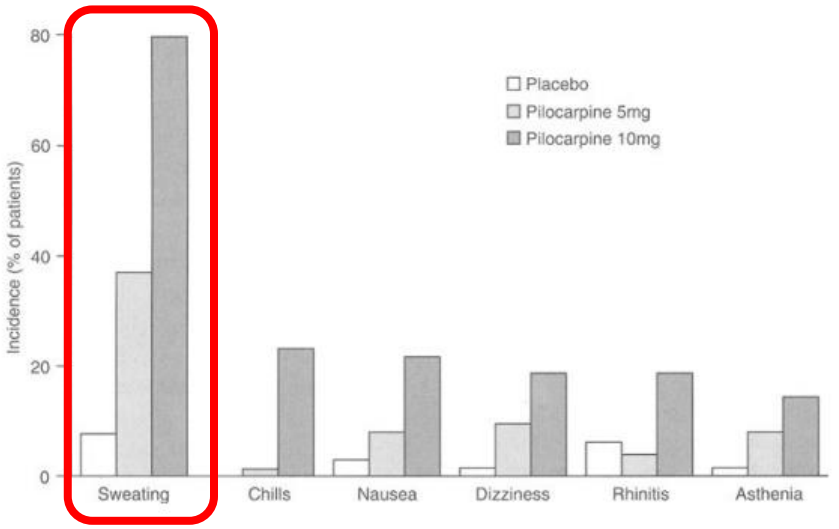
Salivation could recover to the normal level 1h after dosing (Vivino et al., 1999)



Salivation enhancement disappears in ~2 hours (Wiseman and Faulds, 1995)



High incidence of cholinergic adverse reactions e.g., sweating (Wiseman and Faulds, 1995)



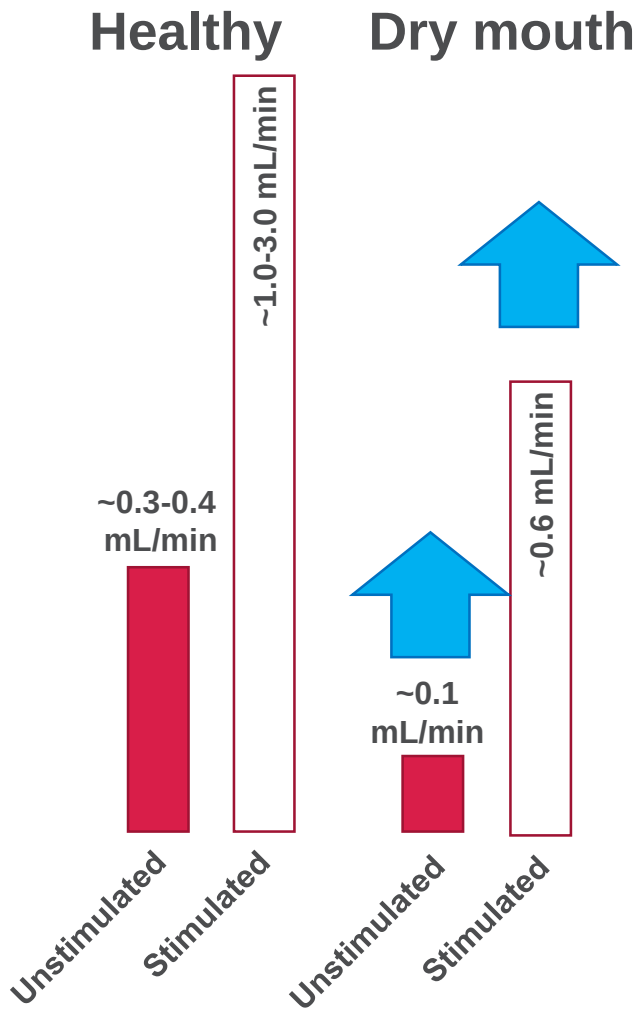
"Severe sweating was the most frequent side effect leading to cessation of therapy" (Noaiseh et al., 2014)

Table II. Failure rates among pilocarpine *vs*. cevimeline users.

	1st time users(n)	Failure due to side effects (1st time users)	All failures (1st time users)	2nd time users (n)	All failures (1st and 2nd time users)	Sweating (All users)
Pilocarpine	59	28/59 (47.4%)	39/59 (66.1%)	13	44/72 (61.1%)	18/72 (25%)
Cevimeline	59	16/59 (27.1%)	22/59 (37.2%)	32	29/91 (31.9%)	10/91 (11%)
p-value		0.02	0.002		<0.001	0.02

MECHANISTIC RATIONALE AND POTENTIAL SUPERIORITY OVER MUSCARINIC AGONISTS

- **Can improve impaired saliva secretion by enhancing M_3 receptor activation through the PAM mechanism**
- **Can be superior to muscarinic agonists in reducing high incidence of cholinergic side effects**



(Pedersen et al., 2018; Karagozogulu et al., 2018; Poon et al., 2014; with some modifications)

NONCLINICAL PHARMACOLOGY: IN VITRO PAM ACTIVITY AND SELECTIVITY

- **Potent PAM activity on M_3 receptors in functional and binding studies**
- **No sign of direct interaction with the orthosteric site**
- **Selectivity over M_1, M_2, M_4 receptors and various other molecules were confirmed, except for PAM activity on M_5 receptors**

Fold Shift of Concentration Response Curve for Carbachol-induced Ca^{2+} Mobilization

Human Muscarinic	M_1	M_2	M_3	M_4	M_5
ASP8302 (Fold shift, μmol/L)	**0.5 @10**	**0.4 @10**	**20.1 @0.3**	**1.2 @10**	**22.7 @0.3**

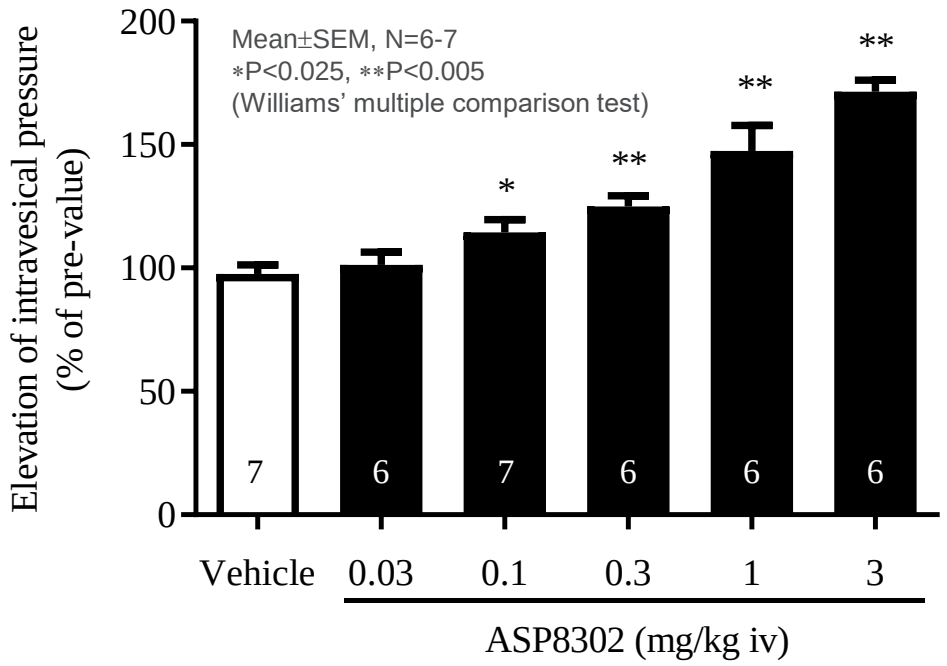
Binding Affinity of Muscarinic Receptor Agonists (from Pharmaceutical Interview Form [IF])

Human Muscarinic	*M_1*	*M_2*	*M_3*	*M_4*	*M_5*
Pilocarpine (Binding IC_{50}, μmol/L)	*8.14*	*6.93*	*5.23*	*54.4*	*40*
Cevimeline (Binding IC_{50}, μmol/L)#	*13.8*	*11.6*	*7.98*	*23.3*	*33.2*

NONCLINICAL PHARMACOLOGY: IN VIVO EFFECTS

- **Effects on bladder and salivary functions were studied in rats**
- **Dose-dependently enhanced nerve stimulation-induced bladder pressure increase**

Potentiation of Pelvic Nerve Stimulation-induced Intravesical Pressure Elevation



NONCLINICAL PHARMACOKINETICS

- **Rats (4 weeks, 10, 60 and 300 mg/kg/day po): C_{max} and AUC_{24} increased with dose increase in both sexes, slightly increased after repeated dosing, higher in females than in males.**
- **Cynomolgus monkeys (4 weeks, 2, 10 and 50 mg/kg/day po): C_{max} and AUC_{24} increased almost dose proportionally in both sexes, no remarkable differences after repeated dosing, no gender differences.**
- **In vitro plasma protein binding: 98.47% to 98.62% in humans, 97.82% to 99.61% in mice, rats, rabbits and cynomolgus monkeys.**
- **Metabolism: no human specific metabolites in hepatocytes.**
- **CYP substrate: CYP2J2 and CYP3A4.**
- **CYP Inhibition: IC_{50} > 75 µmol/L for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A.**
- **Transporter substrate: P-gp and BCRP (not OATP1B1 and OATP1B3 substrate).**
- **Transporter inhibition: IC_{50} 3.79 µmol/L for BCRP, 2.27 µmol/L for OATP1B1, 1.85 µmol/L for OATP1B3, 19.3 µmol/L for OAT1, 12.4 µmol/L for OCT2, 31.6 µmol/L for MATE1, and > 100 µmol/L for P-gp, OAT3, and MATE2-K.**

NONCLINICAL TOXICOLOGY OVERVIEW

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance
Repeat Dose Toxicity	Rat, SD	Oral gavage	1 week	0, 12, 60, 300	No
			1 week	0, 1000	No
			4 weeks	0, 10, 60, 300	Yes
			13 weeks	0, 10, 60, 300	Yes
	Cynomolgus monkey	Oral gavage	1 week	2, 10, 50	No
			1 week	300, 1000	No
			4 weeks	0, 2, 10, 50	Yes
			13 weeks	0, 2, 10, 50	Yes
Genotoxicity	*S. typhimurium* and *E. coli*	In vitro	NA	0, 156 - 5000 µg/plate	Yes
	CHL cell	In vitro	NA	0, 62.5 - 500 µg/mL	Yes
	Rat, SD	Oral gavage	Single	0, 150, 300, 600	Yes
Reproductive and Developmental Toxicity	Rat, SD	Oral gavage	GD7 - 17	0, 30, 100, 300	No
			GD7 - 17	0, 30, 100, 300	Yes
	Rabbit, NZW	Oral gavage	5 days (non-pregnant) GD6 - 18	30, 100, 225 0, 30, 100, 225	No
			GD6 - 18	0, 10, 30, 100	Yes
Phototoxicity	Balb/c 3T3 cell	In vitro	NA	0, 1.22 - 50 µg/mL	Yes
	Mouse, HR-1	Oral gavage	Single	3, 30, 300	No
			Single	0, 3, 30, 300	Yes
	UV-vis spectrum	In vitro	NA	0.025 - 15 mmol/L	Yes

CHL: Chinese hamster lung; *E.coli*: *Escherichia coli*; GD: day of gestation; GLP: Good Laboratory Practice; NA: not applicable; NZW: New Zealand White; SD: Sprague Dawley; *S. typhimurium*: *Salmonella typhimurium*; UV-vis: ultraviolet–visible

NONCLINICAL SAFETY PHARMACOLOGY OVERVIEW

Type of Study	Test System	Method of Administration	GLP Compliance
Central Nervous System	Rat, SD	po	Yes
Cardiovascular	hERG transfected HEK293 cell	In vitro	Yes
Cardiovascular and Respiratory System	Cynomolgus monkey	po	Yes

GLP: Good Laboratory Practice; HEK: human embryonic kidney; hERG: human ether-a-go-go-related gene; po: per os; SD: Sprague Dawley

PHASE 1 CLINICAL STUDY

- **Phase 1 study in healthy volunteers in Europe and Japan demonstrated a favorable safety, tolerability, pharmacokinetic and pharmacodynamic (dose-dependent salivation), profile of ASP8302**
- **Doses up to 150 mg (QD) are safe and tolerated in nonelderly and elderly subjects with comparable exposure (at 150 mg QD). At 150 mg, subjects experienced compound-related adverse events (mainly gastrointestinal symptoms).**
- **A dose-dependent effect on salivation (as pharmacodynamic change) was observed, and the effect was maintained during chronic dosing**
- **Salivation effect was also observed in another Phase 1 study in Japan**
- **Salivation effect was not attenuated after once-a-day multiple administration for 14 days**

astellas

PHASE 2A PROOF OF CONCEPT (POC) STUDY FOR UNDERACTIVE BLADDER (UAB) (8302-CL-0201)

- **Outline: A randomized, double-blind, placebo-controlled, multicenter study in UAB patients (4-week double blind treatment, ASP8302 100 mg or placebo, QD)**
- **Efficacy: The study did not achieve proof of concept in its primary (post void residual urine volume) or key secondary (voiding efficiency) endpoints**
- **Safety: Overall, the safety indicated that ASP8302 was safe and well-tolerated in UAB patients. The number of TEAEs were overall low and mostly mild in severity, and no significant safety signals were observed in other relevant safety outcomes (e.g., ECG, VS, laboratory testing). In the ASP8302 group more drug related TEAEs were reported than in the placebo group, reporting the preferred terms (e.g., gastrointestinal terms including diarrhea and abdominal discomfort, hyperhidrosis) that may suggest relation to the MOA as previously observed in phase 1.**

PHASE 2A PROOF OF CONCEPT (POC) STUDY FOR UNDERACTIVE BLADDER (UAB) (8302-CL-0201)

- **Based on the population PK model, observed plasma ASP8302 concentrations were comparable between P1 and PoC studies, indicating that expected target ASP8302 exposure was achieved in the PoC study.**
- **Conclusion: given the result from this PoC study, development of ASP8302 for UAB was discontinued.**
- **The redacted CSR synopsis for Protocol has been posted on the Astellas Clinical Study Results (ACSR) website: www.astellasclinicalstudyresults.com**

CMC STATUS

Item	Details
Drug Substance	• The remaining of Batch K02 (around 37 kg as a GMP material) can be used if CTM is manufactured before January 2022 • Stability study of Batch K02 (12Mo.:done; 24Mo.: May2021; 36Mo.: May 2022) to be continued • Intermediate for Batch K03 • Reference standard: kept to continue the stability study
Drug Product	• Available formulation: Capsule (used for P1, P2a for UAB)
	• Dose strength(s): 1 mg, 10 mg and 50 mg prepared for UAB
	• Stability data of P1 CTM (up to 34Mo.) and UAB P2a CTM (24Mo.+X) are available
Manufacturing	• CTM manufacturing plan TBD
Others	• Ames (+) impurity (AS192757): can be treated as class 5 (non-mutagenic) with negative in vivo genotoxicity study result

INTELLECTUAL PROPERTY: PATENT COVERING ASP8302

Substance patent

International patent publication: WO2015/186821
Filed : June 2015
Status : Patent covering the substance has been granted in many jurisdictions among which Europe, Japan, USA and China.
Scope : Granted claims cover the ASP8302 substance and its use for UAB.

Indication patent

Priority patent application: Filed 2020
Scope: dry mouth

SUMMARY

- **ASP8302 is a novel PAM of muscarinic M_3 receptors**
- **Wide range of physiological roles of M_3 receptor suggest possible indications, including dry mouth**
- **In vitro and in vivo pharmacology studies, ADME studies, and safety studies have been conducted**
- **ASP8302 enhanced salivation in the Phase 1 clinical study in healthy volunteers**
- **ASP8302 was safe and well-tolerated in the Phase 1 study and Phase 2a study in patients with underactive bladder**
- **Mechanistic rationale and clinical study results suggest a therapeutic potential of ASP8302 for the treatment of dry mouth**

astellas