ASP1617
NON-CONFIDENTIAL SUMMARY

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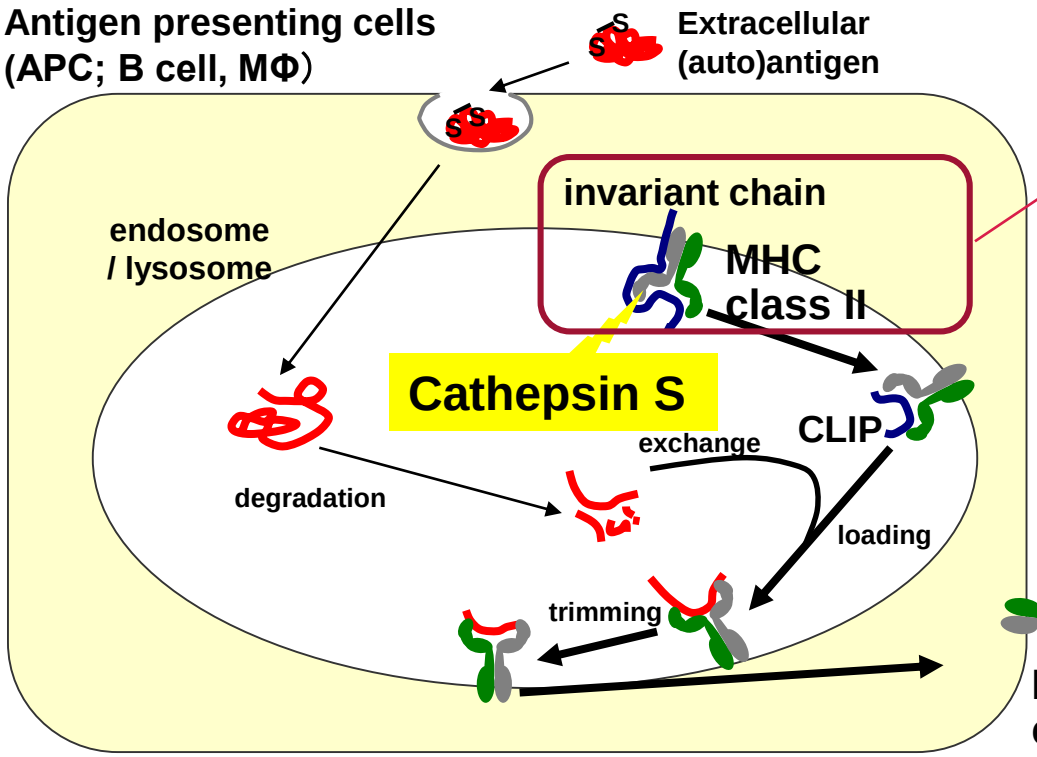
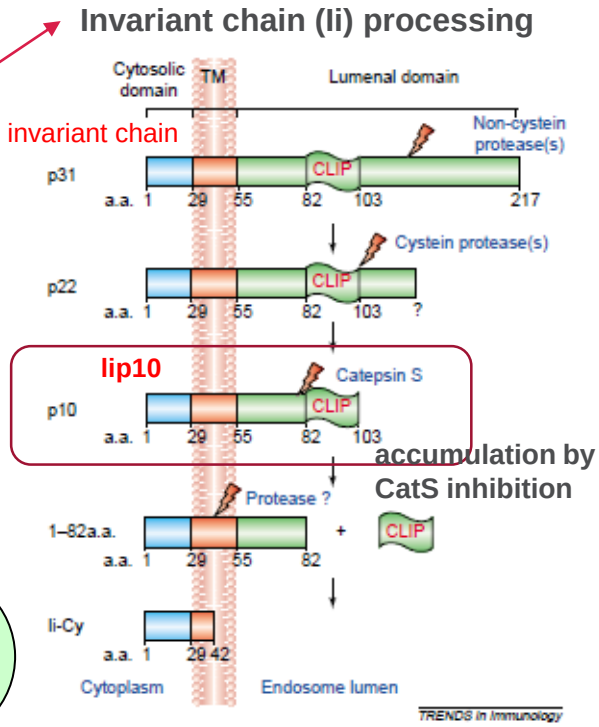
ASP1617 SUMMARY

Items	Note
Product name	ASP1617 disuccinate
Mechanism of Action	Cathepsin S (CatS) inhibitor
Formulation	p.o.
Target Indication at Astellas	Autoimmune diseases (SLE)
Development Territory	Global
Latest development phase	P1 study with healthy volunteers was completed.

Scheme of antigen presentation through MHC class II





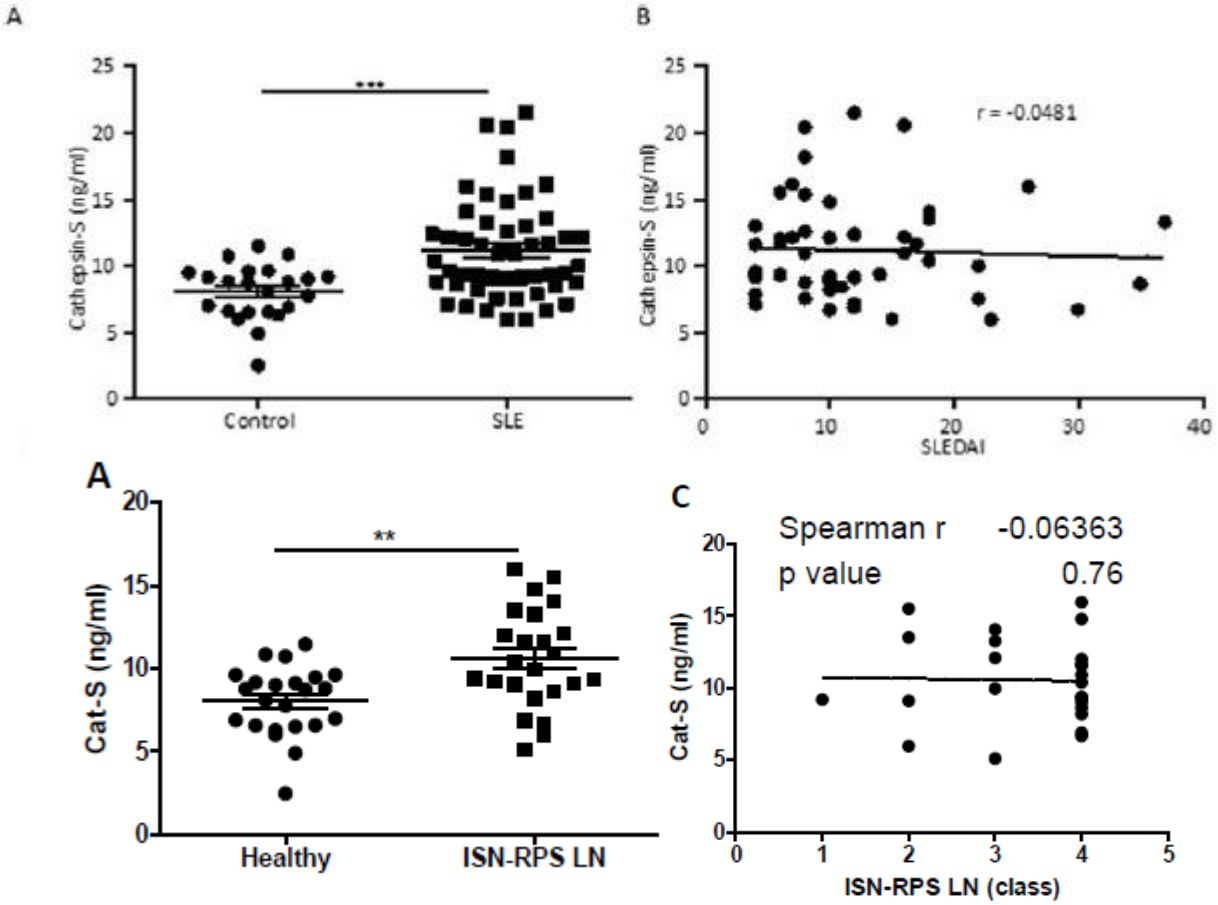
Trends Immunol. **2003** 24 264

Cytokine to help B cell activation

To present antigen peptide onto the cell surface through MHC class II, invariant chain p10 has to be cleaved to CLIP fragment by cathepsin S.

- Cathepsin S inhibitor theoretically inhibits, i) invariant chain degradation, ii) antigen presentation via MHC II, iii) CD4+ T cell activation, iv) B cell activation, and v) antibody production from B cells.

Cathepsin S expression in plasma of SLE/LN



- CatS in plasma was significantly upregulated in SLE and LN patients, but no correlation with disease severity of SLE and LN class was observed.

Sci Rep. 2017 Jun 5;7(1):2775

PHARMACOLOGY
ASP1617 INHIBITS HUMAN/MOUSE CATHEPSIN S WITH HIGH SELECTIVITY

Cathepsin assay

Cat S IC_{50}(nM) Human Mouse	IC_{50}(nM) (selectivity for hCat S) Human Cat K Human Cat L
4.6 0.39	4600 (x1000) 3800 (x830)

Panel assay

Protease (63 proteases） IC_{50}/ Selectivity (hCatS)
Cathepsin B; 6200 nM Cathepsin V; 440 nM Matriptase 2; 7300 nM Papain; 46 nM others; >10000 nM

- ASP1617 inhibits human/mouse cathepsin S with high selectivity.

PHARMACOLOGY
Accumulation of Lip10 in human primary B cells

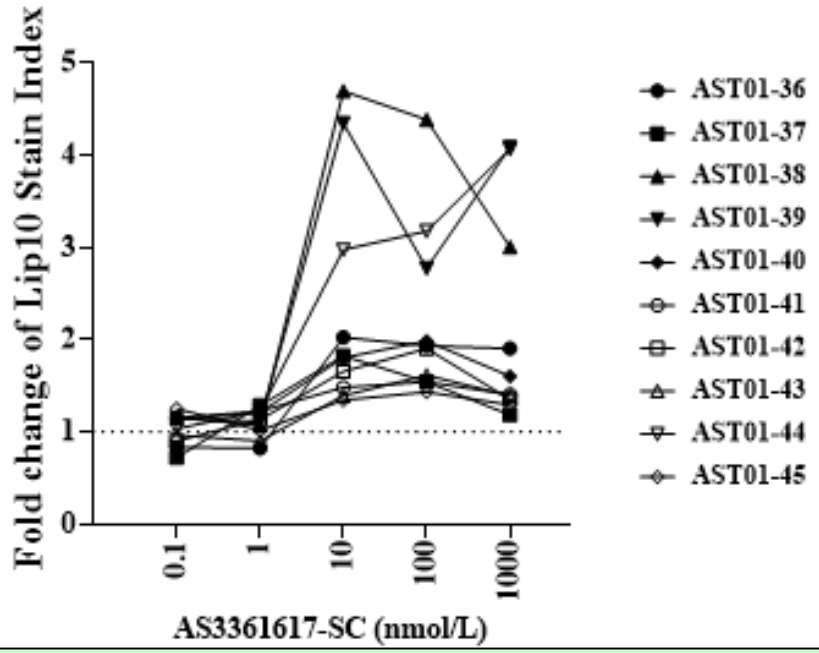
Human B cells from healthy subjects and SLE patients were incubated with ASP1617 without stimulus

*Lip10 stain index; (MFI of CD19+CD20+ B cells) / (MFI of CD3+ T cells)
Fold change of Lip10 stain index; (Lip10 stain index of each AS3361617-SC concentration) / (Lip10 stain index of DMSO control).

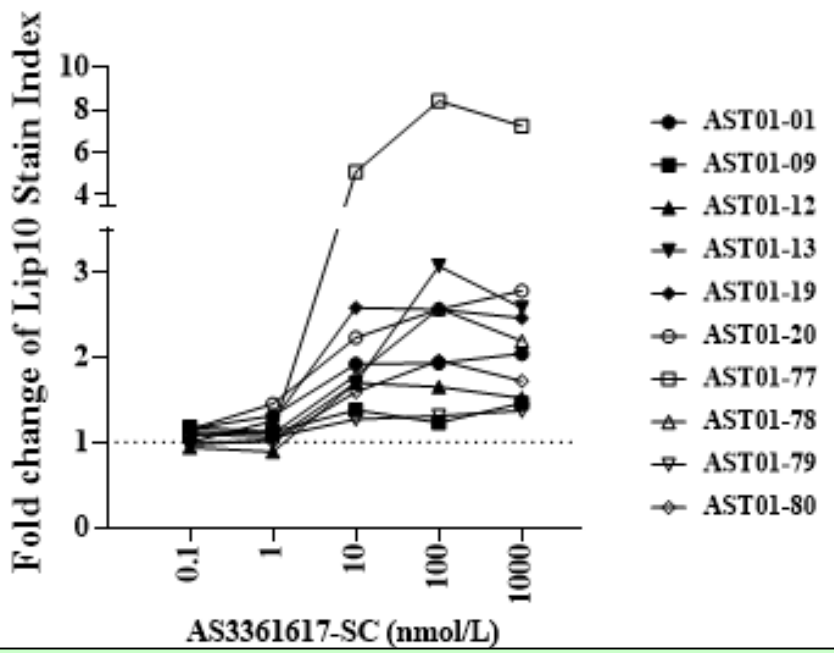
FACS analysis data (Fold change of Lip10 stain index*)

AS3361617-SC; ASP1617 disuccinate

Healthy subjects



SLE patients



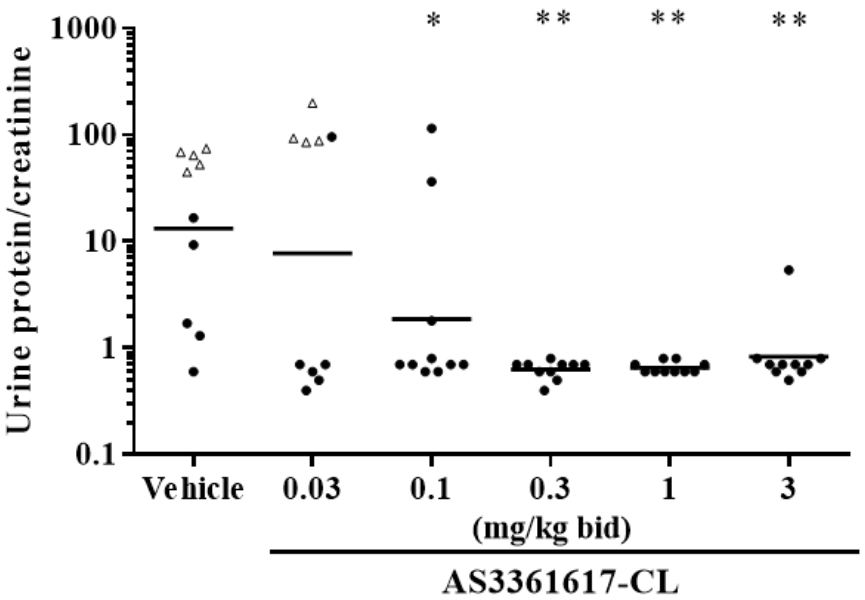
- The treatment with ASP1617 resulted in the accumulation of Lip10 in B cells from both healthy subjects and SLE patients.

PHARMACOLOGY
EFFICACY ON SPONTANEOUS LUPUS PRONE MOUSE MODEL NZB/W F1

- ASP1617 or vehicle was orally administered twice per day (bid) to animals from 20-week-old to 40-week-old.

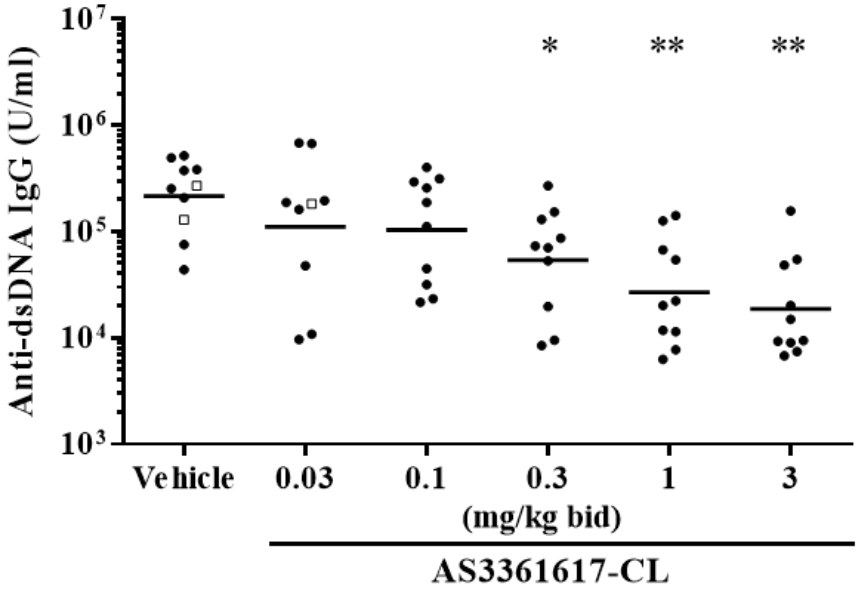
AS3361617-CL; the dihydrochloride salt of the active ingredient of ASP1617

Proteinuria at endpoint



All values are expressed and horizontal lines indicate geometric mean.
* P<0.05 and ** P<0.01 show significant difference analyzed by logarithmic transformation followed by Dunnett's multiple comparison test compared with vehicle group.
Values of withdrawn animals are indicated by open triangles.

Anti-dsDNA IgG at peak



All values are expressed and horizontal lines indicate geometric mean.
* P<0.05 and ** P<0.01 show significant difference analyzed by logarithmic transformation followed by Dunnett's multiple comparison test compared with vehicle group. The geometric mean value in individual mice of 28 and 32-week-old are indicated by closed circle. Values of animals at 28-week old which died between 28 and 32-week-old are indicated by open square.

- ASP1617 showed significant efficacy in a spontaneous lupus prone mouse model.

ADME STUDY LIST

Type of Study	Test system	Method of administration
Absorption		
Single dose, plasma concentration	Rat and Cynomolgus monkey	iv and po
Distribution		
Plasma protein binding	Mouse, rat, rabbit, cynomolgus monkey, human plasma	In vitro
Metabolism		
In vitro metabolism	Mouse, rat, dog, cynomolgus monkey, human hepatocyte	In vitro
Pharmacokinetic Drug Interactions		
In vitro CYP inhibition	Human liver microsomes	In vitro
In vitro UGT inhibition	Human liver microsomes	In vitro
In vitro CYP identification	Recombinant human CYP isoforms	In vitro
In vitro UGT identification	Recombinant human UGT isoforms	In vitro
In vitro transporter inhibition	Transporter expressing cells/vesicles	In vitro

TOXICOLOGY STUDY LIST (1/2)

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance
Single-dose Toxicity					
Single dose (preliminary)	Cynomolgus monkey	Oral gavage	1 day	300, 1000	No
Repeat-dose Toxicity					
1-week repeat dose (preliminary)	Mouse/ Crl:CD1(ICR)	Oral gavage	1 week	0, 30, 100, 300	No
1-week repeat dose (preliminary)	Mouse/ Crl:CD1(ICR)	Oral gavage	1 week	0, 1000	No
4-week repeat dose (pivotal)	Mouse/ Crl:CD1(ICR)	Oral gavage	4 weeks	0, 30, 100, 300	Yes
26-week repeat dose (pivotal)	Mouse/ Crl:CD1(ICR)	Oral gavage	26 weeks	0, 10, 30, 300	Yes
26-week repeat dose (pivotal)	Mouse/ Crl:CD1(ICR)	Oral gavage	26 weeks	0, 100	Yes
2-week repeat dose (preliminary)	Rat/ Crl:CD(SD)	Oral gavage	2 weeks	0, 30, 100, 300	No
13-week repeat dose (preliminary)	Rat/ Crl:CD(SD)	Oral gavage	13 weeks	0, 30, 100, 300	No
1-week repeat dose (preliminary)	Cynomolgus monkey	Oral gavage	1 week	30, 100, 300	No
4-week repeat dose (pivotal)	Cynomolgus monkey	Oral gavage	4 weeks	0, 3, 30, 300	Yes
13-week repeat dose (preliminary)	Cynomolgus monkey	Oral gavage	13 weeks	3, 10	No
26-week repeat dose (pivotal)	Cynomolgus monkey	Oral gavage	26 weeks	0, 3, 10, 100	Yes
Genotoxicity					
Reverse mutation	S. typhimurium and E. coli	In vitro	-	0, 78.1 - 5000 µg/plate	Yes
Chromosome aberration	CHL/IU cells	In vitro	-	0, 12.5 - 500 µg/mL	Yes
Micronucleus test and comet assay	Rat/ Crl:CD(SD)	Oral gavage	3 days	0, 250, 500, 1000	Yes

TOXICOLOGY STUDY LIST (2/2)

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	GLP Compliance
Reproductive and Developmental Toxicity					
Fertility and early embryonic development (pivotal)	Mouse/ Crl:CD1(ICR)	Oral gavage	57 days (male) 22 to 35 days (female)	0, 30, 100, 300	Yes
Embryo-fetal development (preliminary)	Mouse/ Crl:CD1(ICR)	Oral gavage	10 days (GD 6 - 15)	0, 30, 100, 300	No
Embryo-fetal development (pivotal)	Mouse/ Crl:CD1(ICR)	Oral gavage	10 days (GD 6 - 15)	0, 30, 100, 300	Yes
Embryo-fetal development (preliminary)	Rabbit/ Kbl:NZW	Oral gavage	5 days (nonpregnant) 13 days (GD 7 - 19)	100, 300, 1000 0, 10, 30, 100	No
Embryo-fetal development (pivotal)	Rabbit/ Kbl:NZW	Oral gavage	13 days (GD 7 - 19)	0, 10, 30, 60	Yes
Other Toxicity					
Phototoxicity	Balb/c 3T3 cells	In vitro	-	0, 9.49 - 100 µg/mL	Yes

ASP1617 CHARACTERIZATION SUMMARY

- ASP1617 is a selective and potent CatS inhibitor.
- ASP1617 induces Lip10 accumulation in both healthy subjects and patients with SLE in vitro.
- ASP1617 showed significant efficacy in a spontaneous lupus prone mouse model.
- No critical issues in nonclinical studies

Phase 1 study completed

Study title: Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ASP1617 in Healthy Adult Non-Asian and Japanese Subjects Including Assessment of a Food Effect (ClinicalTrials.gov Identifier: NCT04077879)

Study Type: Interventional (Clinical Trial)

Enrollment: 97 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Double (Participant, Investigator)

Start Date: September 19, 2019

Completion Date: June 12, 2021

Study location: California Clinical Trials Medical Group / Parexel, California, United States

Details of the study design can be found on ClinicalTrials.gov Identifier: NCT04077879

INTELLECTUAL PROPERTY

Patent covering ASP1617

- WO2018139438 (filed on Jan 23, 2018)