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GEM045, Autotaxin Inhibitor to treat NASH

Asset Overview

Product Type	Small compound
Indication	NASH (Nonalcoholic steatohepatitis)
Current Stage	Preclinical
Target(MoA)	Autotaxin inhibitor (Abrogation of liver ATX/LPA production)
Brief Description	Lysophospholipid signaling is emerging as a regulator of pathophysiological responses, especially fibrosis. Autotaxin (ATX), a secreted lysophospholipase D (lysoPLD), is responsible for extracellular lysophosphatidic acid (LPA) production. LPA activates multiple G-protein mediated signal transduction pathways leading to responses including the production of pro-inflammatory signals including the stimulation of fibroblast accumulation. Pharmacologic targeting of the ATX/LPA axis using autotaxin inhibitor attenuated fibrotic disease development.
Organization	GEMSEKI Inc.

Differentiation

□ **ATX/LPA production in NASH**

- Abrogation of liver ATX/LPA production resulted in diminished necrosis, apoptosis, and proliferation
- There are relationships between Serum levels of ATX and the Liver Fibrosis Stage with NASH

□ **As an Autotaxin inhibitor, GEM045 showed antifibrotic efficacy**

- GEM045 showed transient half-life but with sustained inhibition of plasma LPA, indicating ATX inhibition dissociated from PK (PK/PD; it shows remarkable PD compared with PK)
- No observations at high MTD dose limit (900 mpk)
- PK study on GEM045 showed only one in-vivo metabolite; LPA reduction plasma assay showed this metabolite has the same activity as GEM045
- GEM045 Showed antifibrotic efficacy with significant histopathological score reductions in NASH (Stelic STAM & MCD) in mice by abrogation of liver ATX/LPA production
- GEM045: LPC-CR IC50 = 36 nM (vs. 234 nM for GLPG-1690 tested in parallel)
- GEM045: LPA reduction (rat plasma) IC50 = 3 nM (vs. 100 nM for GLPG-1690)

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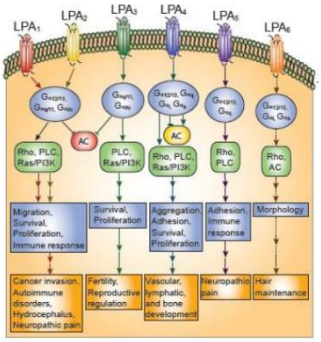
Key Data

The mechanism of LPA action with comparison of Autotaxin inhibitors

	PF-8380	GLPG1690	PAT-409	GEM045
LPC IC_{50}	1.7±0.6	231±62 nM	4 nM	330±73 nM
Plasma IC_{50}	101±0.036 (human)	221 nM (human)	50 nM (human)	10 nM (rat)
NAS • Inflammation • Steatosis • Ballooning	Not available	Not available	-2 • 0 • ≈-1.5 • Not available	-6 • -2 • -2 • -2
Fibrosis	Not available	Not available	-1	-2
Status	Discontinued	Phase 2 (IPF)	Phase 1 ready	IND enabling



Stoddard and Chun, 2015

GEM045 showed significant effects in fibrotic diseases with low MTD

	LPC-CR (in-vitro) IC_{50} (nM)	LPA Reduction (rat plasma) (ex-vivo) IC_{50} (nM)	LPA Reduction % (PD in mice) at 24 hr. (same dosage estimate)	Dog PK	hERG IC_{50} (μM)	CYPs IC_{50} (μM)
GEM045	330	1	Maintained ~80%	$T_{1/2}$ (iv) 7.6 h F% 49.6	>10	>10
GLPG-1690 (Finished Phase II for IPF)	231	100	Dropped to ~30%	$T_{1/2}$ (iv) 3.5 h F% 63	>10	>10

➢ **MTD of GEM045: no findings up to 900 mg/kg, po, b.i.d. for 5 days in mice.**

GEM045 showed significant effects in chronic pancreatitis (Histology Score 11.0 -> 7.4); MCD (NAS 6.4 -> 0.9, Fibrosis 1.9 -> 0.0); Stelic-STAM (NAS 4.5 □ 3.3); CDA-HFD (NAS+Fibrosis Score 8.5 -> 5.4); IPF (Pulmonary Inflammation 3.1 -> 2.1, Pulmonary Fibrosis 4.3 -> 2.7); paw edema (edema volume ↓67%)

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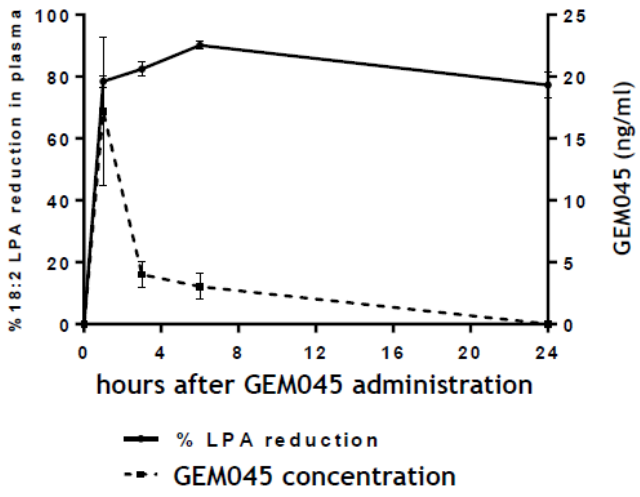
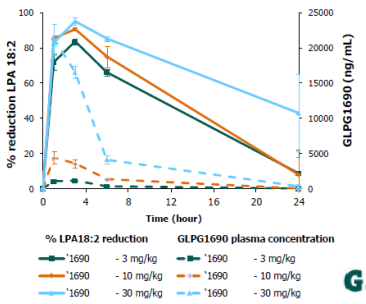
Key Data

GEM045 Mouse PK/PD Properties Reduction of plasma LPA 18:2 as a



1. Compound: GEM045
2. Dose: PO= 20 mg/kg
3. Formulation:
   5% DMSO + 20% Cremophor EL®+ PBS
4. Time point (hour): PO= 0, 1, 3, 6 and 24
5. Analysis: GEM045 and LPA 18:2
   by LC-MS/MS

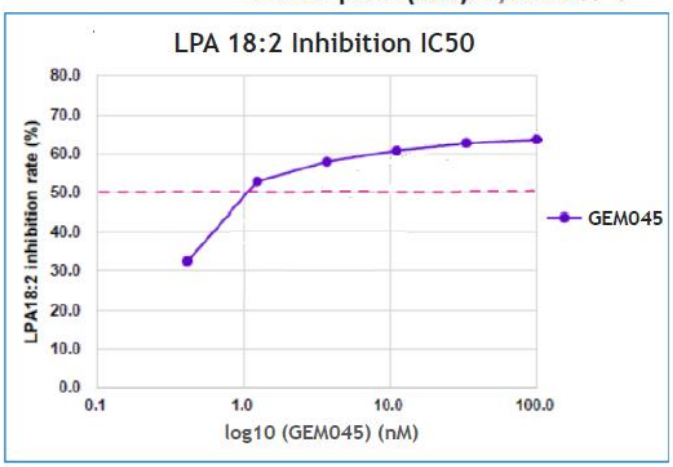


Galápagos

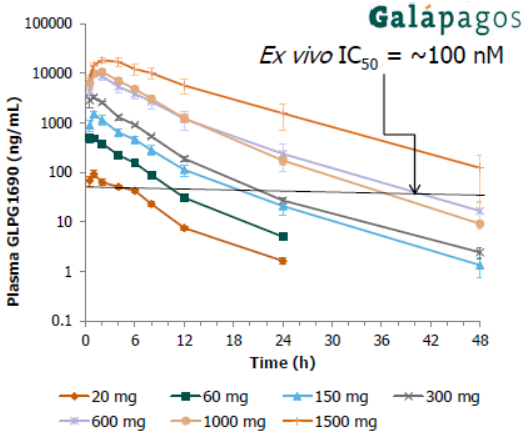
GEM045 showed transient half life but with sustained inhibition of plasma LPA, indicating ATX inhibition dissociated from PK.

LPA 18:2 Inhibition in Rat Plasma of GEM045

Setting:
1. Compound: GEM045
2. Test system : SD rat plasma
3. Concentration (nM): 0, 0.4, 1.2, 3.7,
4. Time point (min): 0, 2h at 37℃



Galápagos



IC_{50} (nM) in rat plasma	
GEM045	1.1

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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