Novel lysine-gingipain inhibitor atuzaginstat (COR388) is efficacious in a mouse model of periodontal disease.

Florian Ermini, PhD[1], Malgorzata Benedyk[2], PhD, Agata Marczyk, PhD[2], Shirin Kapur, PhD[1], Ursula Haditsch, PhD[1], Mai Nguyen, PhD[1], Debasish Raha, PhD[1], Mark Ryder, DMD[3], David Hennings, PhD[1], Michael Detke, MD, PhD[1], Leslie J. Holsinger, PhD[1], Casey Lynch[1], Stephen Dominy, MD[1], Jan Potempa, PhD[2,4]

[1]Cortexyme, Inc., South San Francisco, CA, USA. [2]Jagiellonian University, Krakow, Poland. [3]University of California San Francisco, San Francisco, CA, USA. [4]University of Louisville, Louisville, KY, USA.

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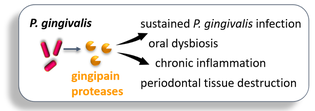
Aim

Porphyromonas gingivalis (Pg) has been identified as a keystone pathogen in the development of periodontal disease (PiD). Gingipain proteases are unique virulence factors expressed by *P. gingivalis* that enable a sustained and chronic infection resulting in oral dysbiosis, increased inflammation and ultimately, periodontal tissue destruction.

Atuzaginstat (COR388) is a highly potent and selective small molecule gingipain inhibitor with oral bioavailability and brain penetration that was developed for the treatment of Alzheimer's disease (AD)[1]. Here, dose dependent efficacy of atuzaginstat was tested in a mouse model of *Pg*-induced PiD.



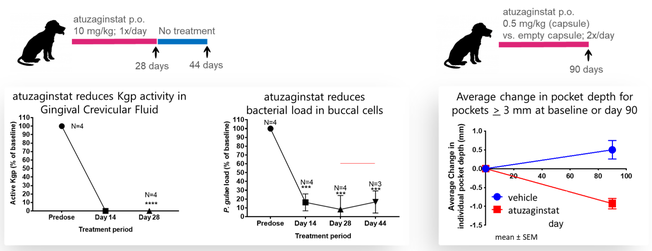
Background

Atuzaginstat characteristics

- Highly selective for lysine-gingipain (Kgp) vs cellular targets
- Orally bioavailable, good tissue distribution, CNS penetrant
- High level of safety established
- No evidence for the development of bacterial resistance
- Engages Kgp in oral biofilms (see new data presented at **IADR General Session 2021 poster# 2121)**

The Kgp inhibitor atuzaginstat is in a phase 2/3 clinical trial for Alzheimer's disease (GAIN) which includes a sub study for periodontal disease (REPAIR). Further information on the design and baseline data of the GAIN and REPAIR studies can be found here: https://ir.cortexyme.com/static-files/4308f6fe-44f3-4128-8ecd-61fb048d916d

Atuzaginstat is efficacious in an aged dog model of periodontal disease



Previously we have investigated the therapeutic potential of atuzaginstat in aged dogs that harbor a natural oral infection with the lysine-gingipain expressing bacteria *P. gulae*[2]. Oral administration of atuzaginstat is efficacious in reducing gingipain activity and bacterial load after 28 days of treatment. Furthermore, in the aged dog model atuzaginstat promotes recovery from periodontal disease indicated by decreasing pocket depth after 90 days of treatment.

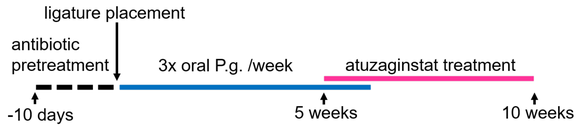
References

1 Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, Nguyen M, Haditsch U, Raha D, Griffin C, Holsinger LJ, Arastu-Kapur S, Kaba S, Lee A, Ryder MI, Potempa B, Mydel P, Hellvard A, Adamowicz K, Hasturk H, Walker GD, Reynolds EC, Faull RLM, Curtis MA, Dragunow M, Potempa J (2019) Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv* **5**, eaau3333.

2 Arastu-Kapur S, Nguyen M, Raha D, Ermini F, Haditsch U, Araujo J, Lannoy IAMD, Ryder MI, Dominy SS, Lynch C, Holsinger LJ (2020) Treatment of Porphyromonas gulae infection and downstream pathology in the aged dog by lysine-gingipain inhibitor COR388. *Pharmacol Res Perspectives* **8**, e00562.

Methods

Experimental Design



- Mice: 8-week-old, female, Balb/c (exp 1, 2), C57BL/6 (exp.3)
- Bacteria: *P. gingivalis* strain W83, 10^9 CFU/100 µL in 2% carboxymethyl cellulose applied to gingiva
- Bilateral ligature placed on second maxillary molar

Dosing

dose group	dose (mg/kg)	dose volume (mL/kg)	route	diluent	remarks	experiment
vehicle	NA	10	p.o.	PBS	Vehicle control	1, 2, 3
moxifloxacin	10	10	s.c.	PBS	Antibiotic	1
COR271	10	10	p.o.	PBS	Kgp inhibitor	1, 2
atuzaginstat	3, 5,10, 30	10	p.o.	PBS	Kgp inhibitor	2, 3

Quantification of Alveolar Bone Loss

- Defleshed maxillae were stained with methylene blue and digital images taken on a stereomicroscope
- The distance of alveolar bone crest (ABC) to cement-enamel junction (CEJ) was measured in ImageJ

Experiment 1: Proof of Concept in Mouse Model

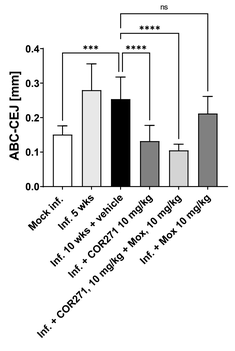
Kgp Inhibitor COR271 Reduces Alveolar Bone Loss in Balb/c mice

To test if the mouse model for alveolar bone loss is suitable to evaluate the efficacy of Kgp inhibitors we first tested the model using COR271, an early-stage irreversible Kgp inhibitor with pharmaceutical properties comparable to atuzaginstat.

COR271 was compared in a head-to-head experiment with moxifloxacin (Mox), a broad spectrum antibiotic.

COR271 was administered p.o., Mox was administered s.c., both compounds were administered b.i.d. at 10 mg/kg.

Key findings:
- The mouse model for P.g. induced alveolar bone loss is suitable for efficacy testing of Kgp inhibitors
- COR271 treatments resulted in the complete recovery of bone loss induced by 5 weeks of P. g infections
- COR271 performed significantly better than moxifloxacin

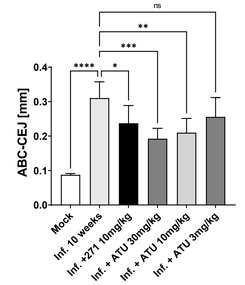


Means with SD; Dunnett's multiple comparison test: ****p< 0.0001, ***p<0.001, ns = not significant

Atuzaginstat is Efficacious at 10 mg/kg, b.i.d.

In a second experiment, we investigated the efficacy and dose-dependence of atuzaginstat (ATU), a compound optimized for clinical use, using a dose ranging from 3 mg/kg b.i.d. to 30 mg/kg b.i.d. A treatment arm of COR271 10 mg/kg b.i.d. was added to compare with the efficacy observed in experiment 1.

Key findings:
- Repeated efficacy of COR271
- Dose response for treatment with atuzaginstat (30 mg/kg > 10 mg/kg> 3 mg /kg)



Means with SD; Dunnett's multiple comparison test: ****p< 0.0001, ***p<0.001, **p<0.01, *p<0.05, ns = not significant

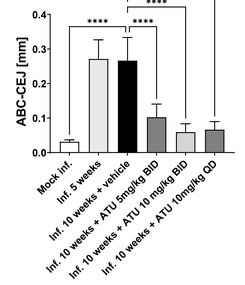
Experiment 3: Efficacy of B.I.D. vs Q.D. Administration

Atuzaginstat is Efficacious at 10 mg/kg, q.d. or 5 mg/kg b.i.d.

In the third experiment we tested the administration regimen of atuzaginstat (ATU): b.i.d. vs q.d..

10 mg/kg b.i.d. was tested against 10 mg/kg q.d. as well as 5 mg/kg b.i.d.

Key findings:
- Oral administration of 10 mg/kg q.d. was equally efficacious as 10 mg/kg b.i.d.
- The effect of 5 mg/kg b.i.d. was highly significant but resulted in slightly less recovery compared to 10 mg/kg b.i.d. or q.d. (70% vs 88% recovery of bone loss, respectively).



Means with SD; Dunnett's multiple comparison test: ****p< 0.0001, ns = not significant

Conclusions

- Oral treatment with atuzaginstat can reverse alveolar bone loss induced by repeated oral infection with *P. gingivalis*.
- These data demonstrate the efficacy of atuzaginstat as a therapeutic in reducing alveolar bone loss and periodontal disease induced by *P. gingivalis* infection and support the further clinical development of this oral therapeutic in the treatment of disease pathologies induced by this bacterial infection including Alzheimer's disease and Periodontal disease.
- These data, combined with mouse, dog and human pharmacokinetic data (data not shown) suggest that a 20 mg daily dose of atuzaginstat may be efficacious against periodontal disease in human subjects.