Inhibition of microsomal prostaglandin E synthase-1 (mPGES-1) by GS-248 reduces prostaglandin E_2 biosynthesis while increasing prostacyclin in human subjects

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Background

Microsomal prostaglandin E synthase-1 (mPGES-1) catalyzes the formation of prostaglandin (PG) E_2 from cyclooxygenase derived PGH_2 ([1,2]).

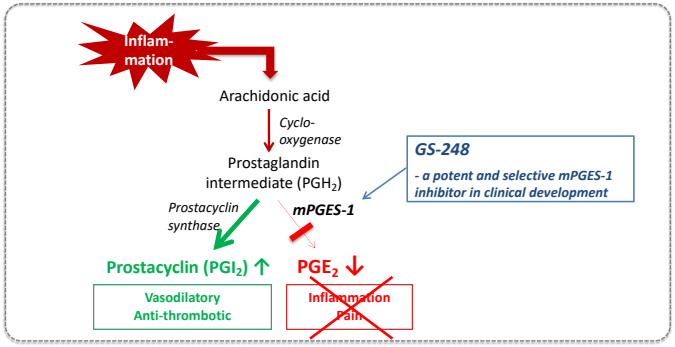
Inhibition of mPGES-1 reduces the pro-inflammatory PGE_2, while concomitantly increasing vasoprotective prostacyclin (PGI_2) via shunting of PGH_2 [3,4] (**Figure 1**).

Therefore, administration of mPGES-1 inhibitors leads to both anti-inflammatory effects in animal models and relaxation of human arteries[4,5].

The prostaglandin profile and pharmacological effects observed following mPGES-1 inhibition, suggest use of such agents for treating inflammatory diseases with concomitant vasculopathies.

GS-248 – potent and selective inhibitor of mPGES-1 exhibiting sub-nanomolar IC_{50} in human whole blood

Figure 1. *Arachidonic acid cascade*



Objective

To evaluate safety, tolerability, pharmacokinetics and pharmaco-dynamics of GS-248 in a clinical phase I study

Methods/assessments

- Safety and tolerability, and GS-248 levels in plasma
- PGE_2 concentrations in *ex vivo* whole blood after LPS incubation
- Excretion of urinary metabolites PGE_2 (PGEM), PGI_2 (PGIM) and thromboxane (TXM)
- Bioanalytical quantification performed by LC-MS/MS.

Study Design

Subjects: Male and female healthy subjects (18-75 years)

Design: Double blind, placebo-controlled and randomised 3:1 (active:placebo)

Dosage: GS-248: 1 - 300 mg single doses (6 cohorts)
20-180 mg, OD; 10 days (3 cohorts)
Celecoxib: 200 mg bid;10 days (8 subjects)

Results

GS-248 administered orally for up to 10 days:

- was safe and well tolerated
- achieved C_{max} 0.5 - 2.5 hours after dosing with a terminal half-life supporting once daily dosage
- completely inhibited mPGES-1-mediated PGE_2 synthesis in the *ex vivo* whole blood assay at 24 hours after single doses (**Figure 2**) with an of IC_{50} ≤0.5 nmol/L
- resulted in reduced renal excretion of PGEM and increased excretion of PGIM and TXM to similar extent (**Figure 3**)

Figure 2. *Inhibition of PGE_2 production in whole blood collected 24h after single oral doses of GS-248 (n=5-6) or placebo (n=8), (mean and SD)*

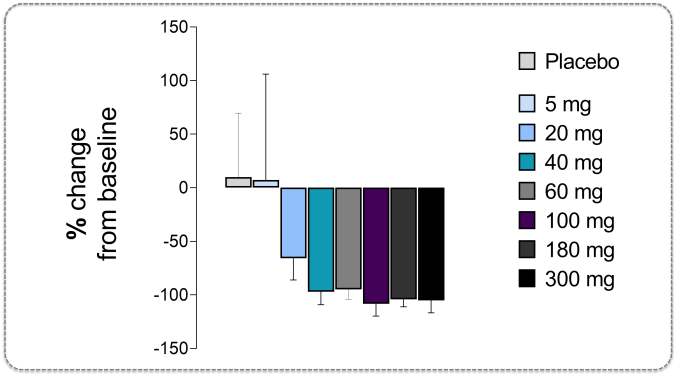
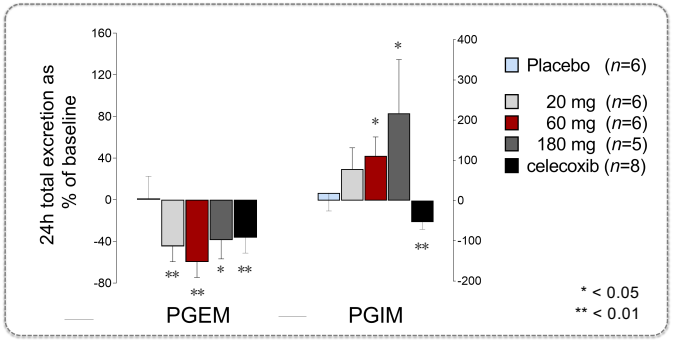


Figure 3. *Change in urinary excretion of prostanoid metabolites after GS-248 or celecoxib treatment for 10 days collected 24 hours post dose (mean and SD)*



Conclusions

- The results indicate that GS-248 affects the arachidonic acid metabolism by inhibiting mPGES-1, thereby shunting the substrate, PGH_2, towards the prostacyclin pathway at doses that are safe and well tolerated
- In contrast, celecoxib, which inhibits cyclooxygenase-2, reduce *both* PGE_2 *and* prostacyclin production
- Elevated prostacyclin production suggests that GS-248 may have vasoprotective effects in addition to the anti-inflammatory and pain-relieving effects expected by reduced PGE_2 production
- The results warrant further evaluation of GS-248 in chronic inflammatory conditions with microvascular disease such as digital ulcers and Raynaud's phenomenon in systemic sclerosis

References:

[1]Korotkova M, Jakobsson PJ. 2014;10:229-41; [2]Bergqvist F et al. POLM 2019;147:106383; [3]Kirkby NS, et al. Cardiovasc Res. 2020; [4]Ozen G, et al. Br J Pharmacol. 2017;174:4087-98; [5]Larsson K, et al. Br J Pharmacol. 2019;176:4625-38

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