Novel Oral Small Molecule FXIIa Inhibitor Blocks Contact System Activation In Vivo

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Disclosure:

E: All authors are employees of KalVista Pharmaceuticals

Introduction

- Hereditary angioedema (HAE) is a genetic disorder that causes recurrent episodes of tissue swelling in the skin and mucosal membranes with a prevalence of approximately 1:50,000[1]
- HAE attacks are caused by uncontrolled plasma kallikrein activity resulting in increased bradykinin (BK) generation, vascular permeability and inflammation[2]
- FXIIa inhibition has been implicated as a novel therapeutic target to prevent the generation of BK in HAE[3]
- Carrageenan-induced paw edema has been used as a preclinical model of bradykinin-mediated angioedema to investigate potential treatments for HAE[4]

1. Lang DM, etal. Ann Allergy Asthma Immunol 2012:109;395-402
2. Banerji A, etal. N Engl J Med 2017;376(8);717-728
3. Craig T, etal. Lancet 2022 Mar 5;399(10328):945-955
4. Kenniston JA, etal J Biol Chem 2014; 289(34):25396

Purpose

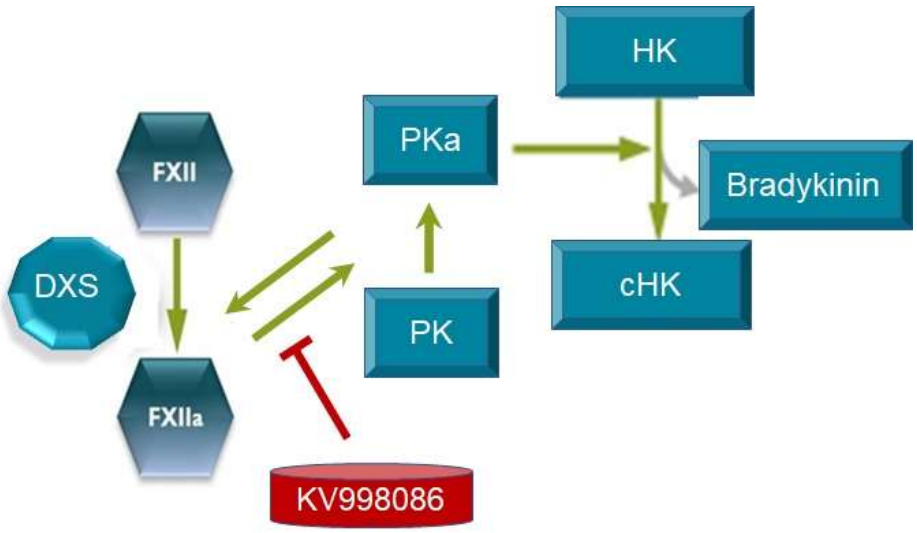
This study evaluated the effects of the oral FXIIa inhibitor KV998086 in carrageenan-induced kallikrein-kinin system activation and angioedema in mice

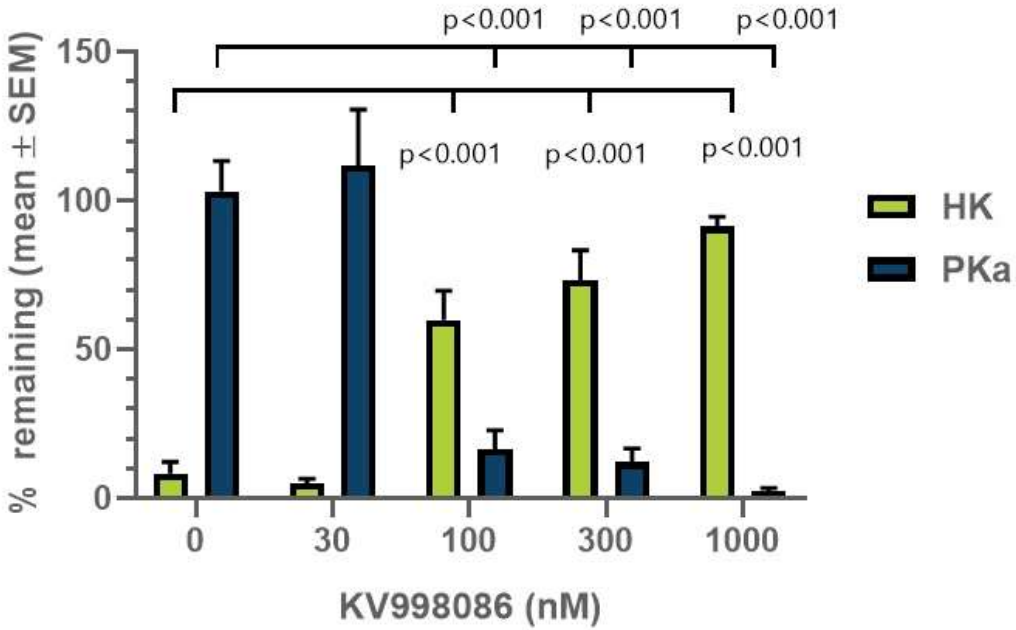
Potency and selectivity of FXIIa inhibitor KV998086

	KV998086
Enzyme	**IC_{50} nM**
Factor XIIa	10.0
Factor Xa	>40000
Plasma Kallikrein	>40000
Thrombin	>40000
Plasmin	>40000
Trypsin	>40000

- KV998086 was selected from a portfolio of potent and selective oral FXIIa inhibitors for *in vitro* and *in vivo* preclinical pharmacology
- KV998086 is highly potent and selective for FXIIa compared to closely related serine proteases

Effects of FXIIa inhibitor KV998086 on dextran sulfate stimulated kininogen (HK) cleavage and plasma kallikrein (PKa) generation in human plasma

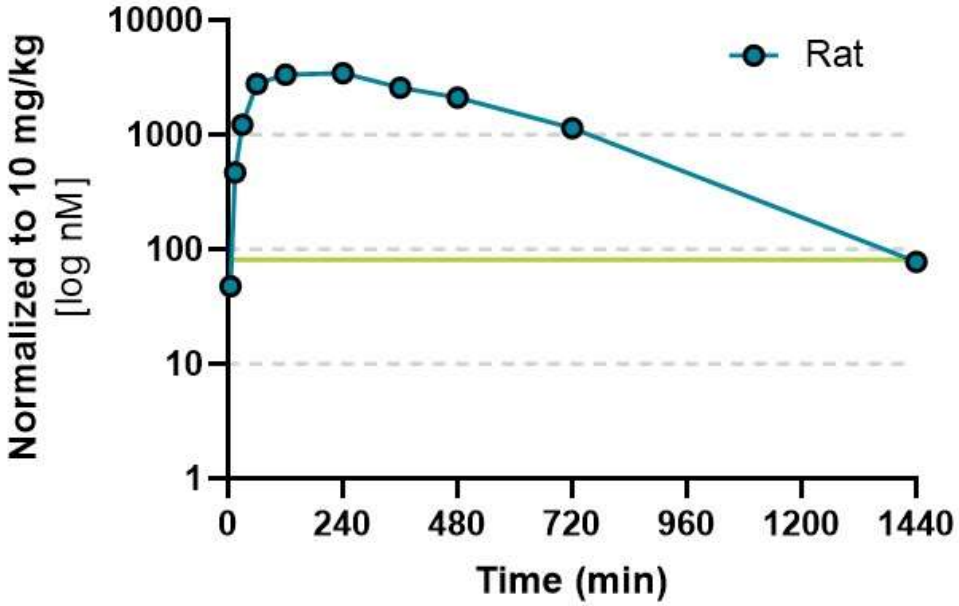


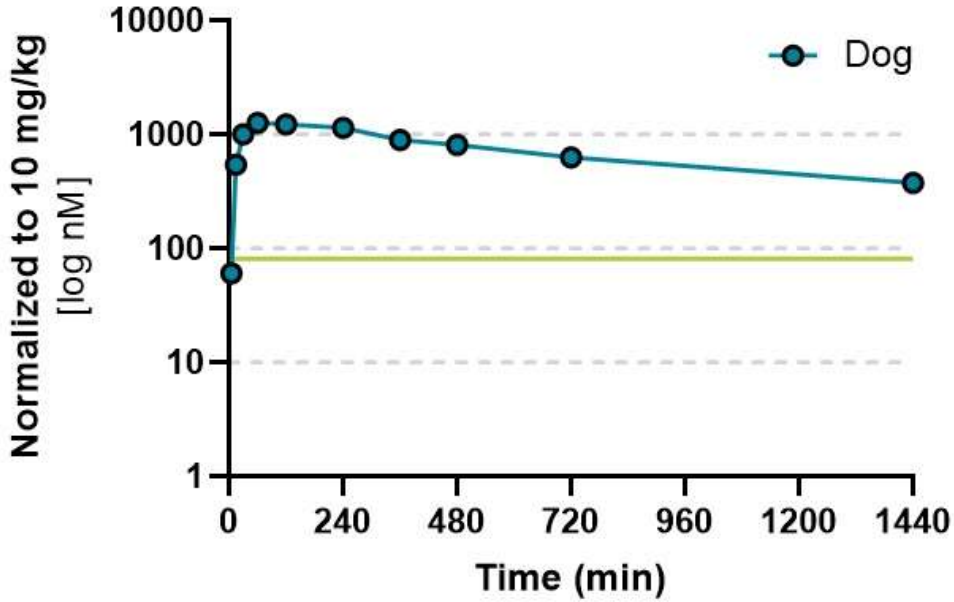


Pretreatment of human plasma with KV998086

- Inhibits HK cleavage with an IC_{50} = 81 nM
- Blocks the activation of plasma prekallikrein (PK) to PKa

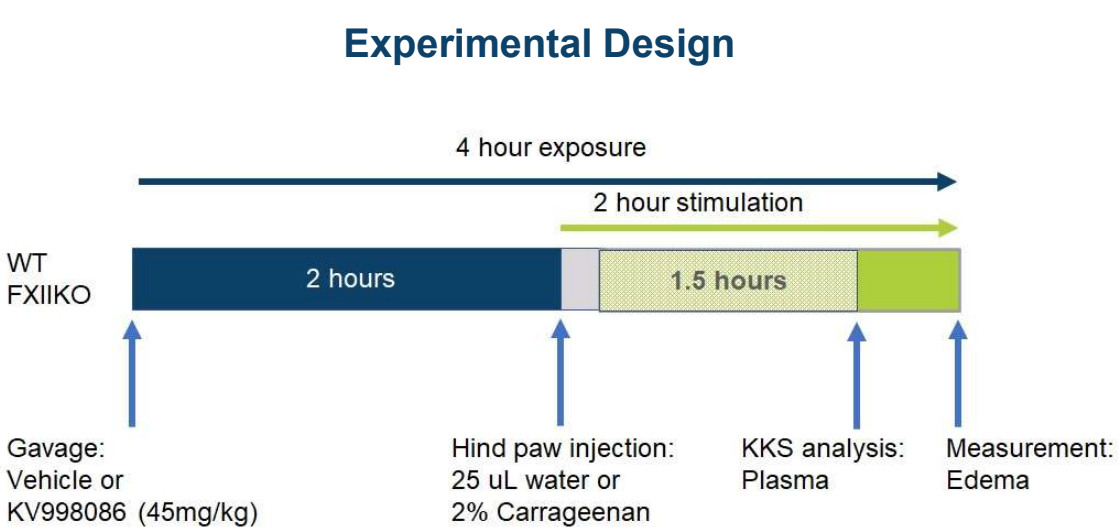
Oral KV998086 pharmacokinetic profiles

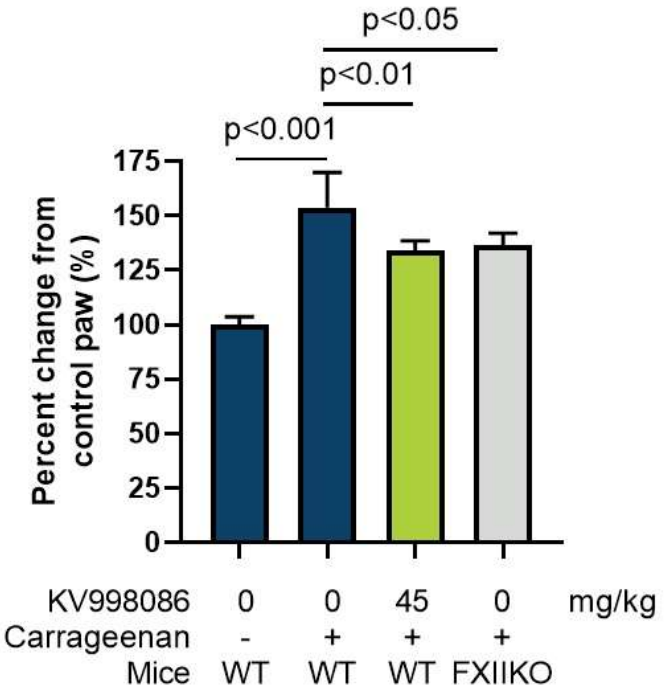




- KV998086 has high oral bioavailability in rat and dog (>70%)
- The IC_{50} of KV998086 for the inhibition of HK cleavage in DXS-stimulated human plasma is indicated by the green lines

Carrageenan (CG)-induced paw edema in mice

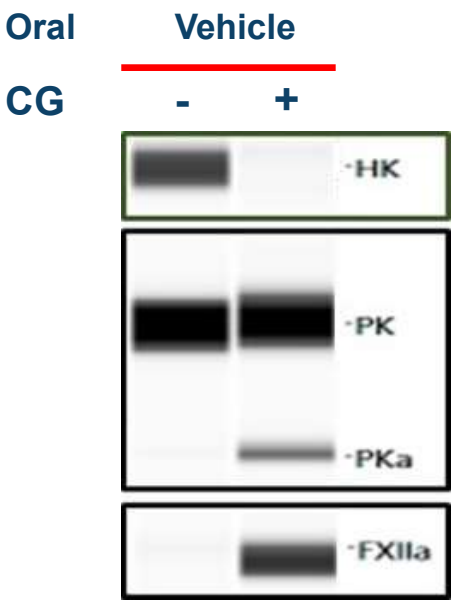




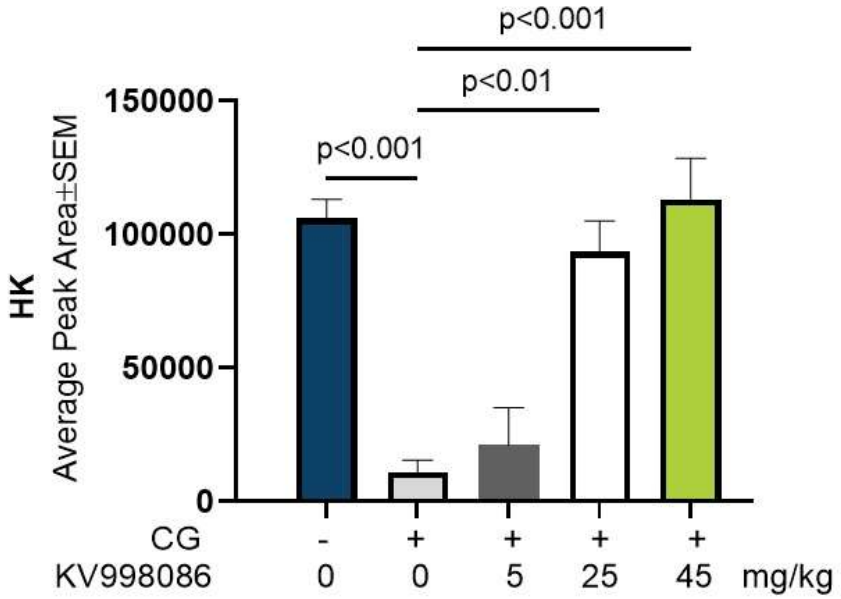
- Oral KV998086 protects mice from CG induced paw edema
- KV998086 is as effective as FXII gene knockout in this model

Effects of oral KV998086 on CG-induced kallikrein kinin system activation and HK cleavage in plasma

Plasma KKS Immunoblot

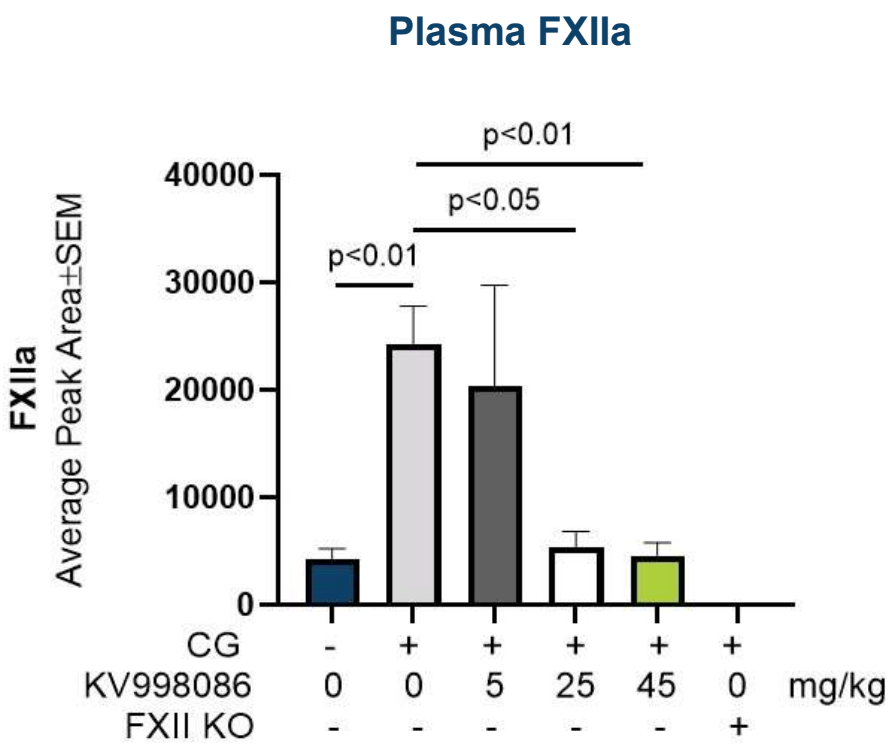


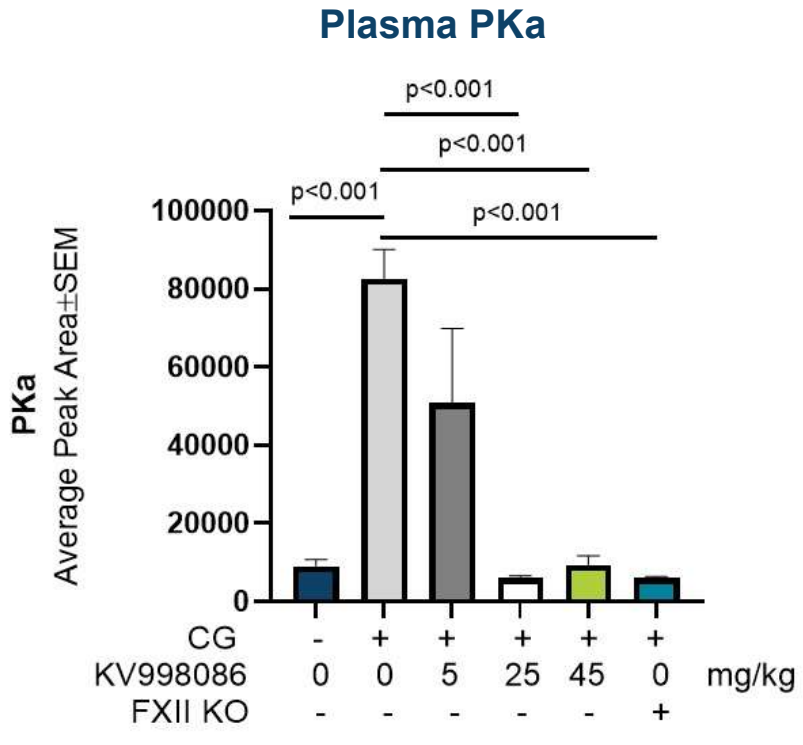
Plasma HK



- Carrageenan (CG) stimulates HK cleavage and increases FXIIa and PKa
- Oral KV998086 protects mice from HK cleavage in a dose responsive manner

Effects of orally KV998086 upon CG-induced generation of FXIIa and PKa





- KV998086 protects mice from PKa and FXIIa generation in a dose-responsive manner
- Oral KV998086 is as effective as FXII gene knockout in protecting mice from CG induced kallikrein kinin system activation

Summary/Conclusions

- KV998086 is a novel potent, selective, and orally available FXIIa inhibitor
  - FXIIa IC_{50} is 10nM and highly selective compared with related serine proteases
  - The IC_{50} for DXS-stimulated HK cleavage in whole human plasma is 81 nM
  - High oral bioavailability demonstrated in both rat and dog
- Preclinical studies in the mouse model of carrageenan induced angioedema showed:
  - KV998086 protected mice from paw edema comparable to FXII knockout
  - KV998086 inhibited the generation of FXIIa & PKa and HK cleavage in a dose-responsive manner
- Oral KV998086 may provide a therapeutic opportunity to block kallikrein-kinin system activation and prevent angioedema attacks in HAE

Thank you

Authors:

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