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Title: Inhibition of ATP-gated P2X3 channels by AF-219: An effective anti-tussive mechanism in chronic cough

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Body: Background Pre-clinical studies suggest that P2X3 receptors are expressed by airway vagal afferents and contribute to the hyperexcitability of sensory neurons. We hypothesized that P2X3 receptors play a role in the sensitisation of vagal pathways mediating the cough reflex leading to chronic cough (CC). Objective To investigate the efficacy of a first in class oral P2X3 antagonist, AF-219, in reducing daytime cough in idiopathic/treatment-resistant CC. Methods 24 subjects (19 women, mean age 54.5 years) were randomised into a double blind, placebo-controlled, 2-period, crossover study, of AF-219, 600 mg bd. Cough was assessed at baseline and after 2 weeks of treatment; primary endpoint, daytime objective cough frequency (coughs/hr) (VitaloJAK™); secondary endpoints, cough severity and urge to cough visual analogue scales (VAS), cough quality of life questionnaire (CQLQ). Results AF-219 markedly and significantly reduced cough (mean difference vs. placebo): daytime cough rate -75% (95%CI -50 to -88), p< 0.001 (Figure 1); daytime cough severity VAS -26mm (-10 to -42), p=0.003; urge to cough VAS -21mm (-2 to -41), p=0.035; and CQLQ -9.2 (-1.7 to -16.8), p=0.018. There were no significant period or carryover effects.

Conclusion P2X3 receptors appear to play a key role in mediating cough neuronal hypersensitivity and their antagonists represent a promising new class of effective anti-tussives.