LONG-TERM TREATMENT WITH CHF5074, A NOVEL γ-SECRETASE MODULATOR, MARKEDLY REDUCES BRAIN β-AMYLOID IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

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A subset of NSAIDs has been shown to allosteric modulate the activity of γ-secretase, the enzymatic complex responsible for the formation of β-amyloid (Aβ), independently from their cyclooxygenase (COX) inhibiting activity. CHF5074 is a new flurbiprofen analogue (1) devoid of anti-COX activity and with potent *in vitro* inhibitory activity on Aβ42 secretion (2). We evaluated the effects of long-term treatment with CHF5074 on brain Aβ pathology in transgenic mice (Tg2576) carrying the double Swedish mutation of APP.

Nineteen Tg2576 mice of 9.5 to 13.0 months of age, were treated with CHF5074 (375 ppm in the diet) for 17 weeks. Eighteen age-matched Tg2576 mice (controls) received standard diet.

Long-term exposure to CHF5074 was well tolerated by Tg2576 mice as no deaths were observed in the treated group and body weight gain of the two groups were similar. There were no abnormal findings at the histopathological examination of main peripheral organs (liver, kidneys, spleen, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum) of CHF5074-treated mice. CHF5074 was well absorbed and reached high concentrations in the brain (2,1 ± 0.1 μg/g). Brain Aβ40 and Aβ42 levels were measured by ELISA after sequential extraction with SDS (2%) and formic acid (70%). Analysis of variance indicated that compared to controls, CHF5074 significantly reduced brain Aβ40 (-45.1 ± 8.8%, $p = 0.028$) and Aβ42 (-39.4 ± 9.1%, $p = 0.044$) levels. The effects in younger animals (9.5 months at beginning of treatment) was more marked (-50.3 ± 9.5% on Aβ40, $p = 0.009$ and -45.0 ± 9.9% on Aβ42, $p = 0.022$). Brain histopathological evaluations, including amyloid plaque load, are underway.

In conclusion, chronic CHF5074 treatment significantly reduced brain Aβ levels in Tg2576 transgenic mice. This novel γ-secretase modulator has, therefore, the potential to be a safe and promising therapeutic agent for AD treatment.

1) Peretto I., Radaelli S., Parini C., et al. (2005) J. Med. Chem. 48: 5705-5720.
2) Imbimbo B.P., Del Giudice E., Cenacchi V., et al. (2007) Pharmacol. Res. (in press).