Sigma-1 Receptor Target Occupancy Study with Dynamic PET Scan Analysis of ANAVEX®2-73, a Clinical Candidate for Neurodegenerative and Neurodevelopmental Diseases

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BACKGROUND

ANAVEX®2-73, a selective sigma-1 receptor (S1R) agonist, has undergone testing in a Phase 2a trial of Alzheimer’s disease patients. Over a period of 57 weeks, ANAVEX®2-73 demonstrated a favorable safety profile and a concentration-dependent improvement against exploratory endpoints MMSE and ADCS-ADL. Positron emission tomography (PET) with [18F]FTC-146, a novel S1R radiotracer, was used in the current study to substantiate target engagement in mice.

MATERIALS & METHODS

Radiochemistry: [18F]FTC-146 was prepared with an automated synthesis module. Analect Inc., Houston, TX, USA

PET Scanning and Autoradiography Procedure: ANAVEX®2-73 was administered orally in 4 dose groups (0, 1, 10, 30 mg/kg) with N=4-5 per group. Mice were anesthetized using isoflurane 20 minutes after administration of ANAVEX®2-73 and tail vein catheters were inserted. After 60 minutes post-drug delivery, [18F]FTC-146 (210±22 µCi, 7.7±0.81 MBq) was injected intravenously and a dynamic PET scan (Siemens Inveon D-PET, 60 minutes) was performed (Figure 1). Following the PET scan, the mice were perfused and the brains were collected and sectioned at 20 µm for ex vivo autoradiography (ARG). The brain regions collected were: frontal cortex, caudate, hippocampus, thalamus, amygdalar, cingulate, and cerebellum for normalization.

Metabolism Correction Procedure: Separate mice (N=6, 0 mg/kg ANAVEX®2-73) were used to derive the whole blood to plasma ratio and parent fraction for metabolite correction. Whole blood IDIF was described by a 3-exponential model. The two-tissue compartment kinetic (2TCM) modeling was performed in the whole brain using PMOD 3.7. To measure arterial whole blood input function (IDIF) was gathered from the left ventricle of the heart. The hottest pixels were used to define IDIF. For receptor occupancy calculations, the k_e/k_m macro parameter was used for binding potential. SUV was also used to assess target engagement of ANAVEX®2-73 with the S1R. To analyze ex vivo ARG, ImageJ was used to define regions of interest and all structures were normalized to muscle.

RESULTS

For [18F]FTC-146 production², the molar radioactivity was 12.8 ± 5.7 Ci/mmol (474 ± 211 GBq/mmol) and radiochemical purity was 91-94% at the end of synthesis. The two-tissue compartment model was successfully fitted to the 60-minute dynamic mouse brain data (Figure 2). The whole blood IDIF was described by a 3-exponential model. After 5 minutes post-injection, 16% of counts in plasma could be attributed to the parent radioligand. The data suggested a fixed correction of 1.114 for whole blood counts to plasma. Model macro parameters and receptor occupancy calculations are summarized in Table 1. PET data shows S1R occupancy is dose-dependent for ANAVEX®2-73 with a plateau at 68% ± 11% in whole brain (Figure 3). For analysis of ex vivo ARG, selected brain regions (frontal cortex, caudate, hippocampus, thalamus, amygdalar, cingulate, cerebellum) were analyzed and receptor occupancy ranged from 30-60% (Figure 4). These results were compared with PRE-084, a well-known S1R agonist.

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REFERENCES