# Determination of $^{18}$F-FMAU Viability in Tumor Progression

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## Background/Purpose

Glioblastoma (GBM) is a highly aggressive cancer type that originates in the brain. Despite available treatments, patients with Glioblastoma have a 5-year survival rate of 6.9%, largely due to pseudo-progression. Tumor pseudo-progression is the phenomenon where treatment causes residual tumor enlargement and increased contrast enhancement uptake, mimicking tumor progression, in the absence of true tumor growth. Current tools have proven inconclusive in differentiating pseudo-progression, leading to consequences, such as premature treatment discontinuation and increased patient risk. The molecular imaging tool 2'-Deoxy-2'-[18F]fluoro-5-methyl-1-β-D-arabinofuranosyl uracil ($^{18}$F-FMAU) has shown promise in collecting PET Imaging data and potential to differentiate tumor progression.

## Methods

GastroPlus was used to perform Physiologically based Pharmacokinetic (PBPK) modeling and simulate changes of $^{18}$F-FMAU drug plasma concentrations over time. A literature search of $^{18}$F-FMAU was conducted with little evidence of relevant published studies associated with $^{18}$F-FMAU administration. The stereoisomer Clevudine (L-FMAU) was substituted in place of $^{18}$F-FMAU for modeling purposes, due to GastroPlus ignoring stereochemistry. Currently however, Clevudine studies have been limited to rats. To overcome this, a rat model was developed based on assumptions derived from the literature study and converted to a theoretical human model using GastroPlus. Following this, a PBPK model unique to each of the 10 patients was generated, factoring in each patient's age, weight, BMI, and ethnicity.

## Results

In all patients, strong correlation was found between simulated GastroPlus blood plasma concentrations and data obtained from the previous study involving human administration of $^{18}$F-FMAU. PET Scans, from a prior study, depicting high levels of contrast enhancement within the first minutes mirrored GastroPlus predictions of high blood plasma concentrations in the carotid artery during the distribution phase. Similarly, the elimination phase where $^{18}$F-FMAU was cleared from the carotid artery coincided with lower levels of contrast enhancements after time had passed. The volume at steady state (Vss) and clearance (CL) of $^{18}$F-FMAU was also estimated to be 85 L and 5.8 L/hr, respectively. The average linear regression $r^2$ value of 0.793 between observed and GastroPlus predicted $^{18}$F-FMAU concentrations suggests strong statistical significance, as a value greater than 0.6. Overall, this supports the initial hypothesis that $^{18}$F-FMAU follows two-compartment pharmacokinetics.

## Conclusion

Findings from this study allows us to predict, at some level, plasma concentrations of $^{18}$F-FMAU in any patients with a variety of demographics. This study also establishes that the 1-hour imaging period normally reserved for imaging represents the distribution phase of $^{18}$F-FMAU and that the radiotracer's elimination phase extends well beyond the imaging period, which changes how drug accumulation will be monitored.