A Generic Tacrolimus Capsule Shown Not to Be Bioequivalent to the Brand Tacrolimus Capsule in a Post-approval Pharmacokinetic Bioequivalence Study in Healthy Subjects

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BACKGROUND:

- Tacrolimus, a narrow therapeutic index (NTI) immunosuppressant, is a poorly water-soluble drug. The reference listed drug (RLD), PROGRAF and its generic products including Accord Healthcare's (AH) tacrolimus capsules are designed to contain amorphous tacrolimus to enhance tacrolimus bioavailability.
- A previous FDA-funded research study found AH's product to be unstable as it crystallized under accelerated storage conditions while the RLD maintained its amorphous form.
- A post-approval in vivo pharmacokinetic (PK) bioequivalence (BE) study was conducted to evaluate BE of AH's product (Test) to its RLD.

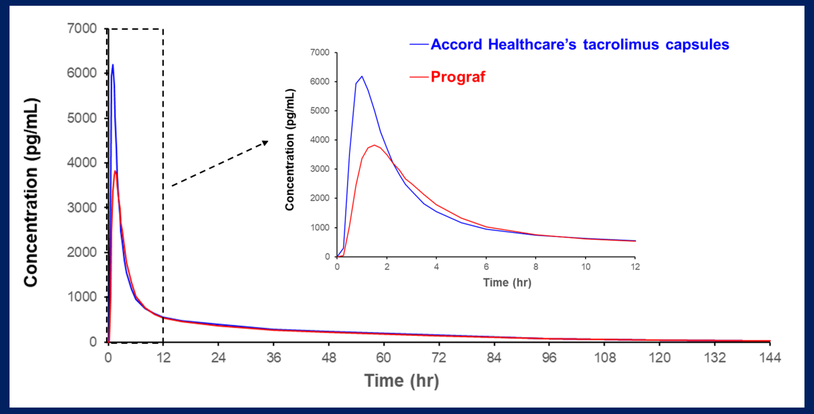
METHODS:

- A single-dose, randomized, open-label, two-treatment, two-sequence, four-period, fully replicated crossover BE study was conducted under fasting conditions.
- Sixty-seven healthy subjects received fresh (i.e., no crystalline was detected) RLD 1 mg and Test 1 mg.
- Tacrolimus concentrations in whole blood were determined using the liquid chromatography with tandem mass spectrometry method. The BE assessment was based on FDA's NTI criteria.

RESULTS:

- Sixty-two of 67 subjects were included in the PK and statistical analyses.
- Using the unscaled average BE procedure, the 90% confidence interval (CI) for area under the curve from time zero to 72 hours (AUC_{0-72}) and maximum plasma concentration (C_{max}) were 106.04% – 124.76% and 157.38% – 188.17%, respectively.
- Using the reference-scaled average BE procedure, the 95% upper confidence bounds were less than 0 for AUC_{0-72} (i.e., -0.043) but greater than 0 for C_{max} (i.e., 0.365).
- The upper limit of the 90% CI for the ratios of within-subject standard deviation of Test and RLD was less than 2.5 for both AUC_{0-72} (i.e., 0.2997) and C_{max} (i.e., 0.2080).
- It is expected that Cmax of Test decreases when amorphous tacrolimus crystallizes over time resulting in variable BE conclusions.
- The most common AEs were headache, toothache, vessel puncture site pain, nasal congestion, and hypertension.

Accord Healthcare's tacrolimus capsules exhibited higher maximum plasma concentration (Cmax) than its reference listed drug, PROGRAF.



In Sept 2023, **FDA changed the therapeutic equivalence rating for Accord Healthcare's tacrolimus capsules from AB (drug products are therapeutically equivalent) to BX (not automatically substitutable at the pharmacy).**

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Summary of demographic characteristics

Characteristics	Test product	Reference product
Subject number	66	64
Mean age (years, range)	39.1 (24-59)	39 (24-59)
Gender, n (%)		
Male	45 (68.2)	44 (68.8)
Female	21 (31.8)	20 (31.3)
Race, n (%)		
American Indian or Alaska Native	2 (3)	2 (3)
African American	51 (77.3)	50 (78.1)
Caucasian	13 (19.7)	12 (18.8)
Ethnicity, n (%)		
Hispanic or Latino	2 (3)	2 (3)
Not Hispanic or Latino	64 (97.0)	62 (96.9)

Descriptive statistics of PK parameters for tacrolimus in whole blood

PK parameters	Test product	Reference product
C_{max} (pg/mL)$^{\kappa}$	6780.05 (± 2830.05)	4246.68 (± 2243.37)
AUC_{0-72} (pg.h/mL)$^{\kappa}$	37434.51 (± 20086.16)	33716.80 (± 19885.62)
AUC_{0-inf} (pg.h/mL)$^{\kappa}$	45484.38 (± 25524.52)	42764.68 (± 25066.88)
T_{max} (h)$^{\delta}$	1.00 (0.50 - 2.75)	1.50 (0.75 - 4.03)
$T_{1/2}$ (h)$^{\omega}$	36.81 (18.49 - 62.66)	37.64 (21.16 - 54.93)

$^{\kappa}$ Presented as mean (± standard deviation) $^{\delta}$ Presented as median (minimum - maximum)
$^{\omega}$ Presented as mean (minimum - maximum)

Results of unscaled average and reference-scaled BE analysis

PK Parameters	S_{WT}	S_{WR}	Ratio (S_{WT}/S_{WR})	90% CI Upper Limit for S_{WT}/S_{WR}	Test/Reference Geometric Mean Ratio (90% CI) (%)	95% Upper Confidence Bound
C_{max}	0.2244	0.2080	1.08	1.38	172.09 (157.38 - 188.17)	0.365
AUC_{0-72}	0.3000	0.2997	1.00	1.31	115.02 (106.04 - 124.76)	-0.043
AUC_{0-inf}	0.2961	0.2908	1.02	1.33	111.91 (102.48 - 122.20)	-0.049

S_{WT}: Within-subject standard deviation for test
S_{WR}: Within-subject standard deviation for reference

Summary of most common (>3% of subjects) adverse events

	Test; N=66 (Incidence (%))	Reference; N=64 (Incidence (%))
Headache	7 (10.6%)	5 (7.8%)
Toothache	0 (0%)	2 (3.1%)
Vessel puncture site pain	0 (0%)	2 (3.1%)
Nasal congestion	2 (3.0%)	0 (0%)
Hypertension	1 (1.5%)	2 (3.1%)

Disclaimer: The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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