INTRODUCTION

- MPH (methylphenidate) is commonly prescribed for the treatment of attention-deficit hyperactivity disorder (ADHD) in children.
- Due to its rapid metabolism, clearance, and abuse liability, once-daily modified-release formulations have been designed to achieve specific plasma concentration profiles of MPH which provide a full day of symptom control while reducing the abuse-related potential.
- MPH provides twice or threefold higher peak plasma concentrations compared to the immediate release product OROS®-MPH.
- Therefore, it is important that generics deemed bio-equivalent show a release profile that is consistent with the reference product throughout the dosing interval.

OBJECTIVE

- To assess the bioequivalence of MPH-ER-C® (54 mg) with MPH-SR (60 mg) in a randomised, single-dose, 2 way crossover study in healthy volunteers.

METHODS

- In Vitro: Dissolution tests were performed on 3 tablet types: 5mg OROS®-MPH, 20mg MPH-SR, and 54mg OROS®-MPH-C® at pH 1.2 in accordance with USP 32 monograph for methylphenidate hydrochloride Extended Release Tablets (Test 1) using dissolution Apparatus 2 and validated on Appendix 7. Dissolution profile comparison were conducted using the f2 10 formula. 
- In Vivo: Subjects were males and females between 18 and 45 years of age inclusive; body mass index (BMI) between 18.0 and 30.0 kg/m², inclusive and a body weight of no less than 53 kg.  

Treatment Periods

- Volunteers were requested at the clinical site from the evening before first dose until the collection of the 24-hour urine samples for each of the three treatment periods. 
- Periods were: 1) planning of 31 days; 2) receiving a single dose of 54-mg OROS®-MPH-C®, a single dose of 30mg immediate-release MPH-SR (5 mg of a 5 mg MPH-SR); and 3) safety assessments were performed after 24-hour period.

RESULTS

- AUC ratio: Statistical analysis of A and T times were performed on raw data, while overall, males and females and all subjects were compared prior to analysis using a mixed-effect analysis of variance model with treatment, period, and treatment sequence as fixed effects, and subject as a random factor.


d-MPH: Selected summary and inferential statistics of derived PK parameters of d-MPH following oral administration of 54-mg OROS®-MPH, 20mg MPH-SR, and 5mg MPH-SR, Evaluable Population

| | Cmax (ng/ml) | λ (h) | Cmax/λ (h) | T1/2 (h) | Mean Plasma Concentration-Time Profiles of MPH (mg) which provide a full day of symptom control while reducing the abuse-related potential.

Safety

- There were no serious or life-threatening treatment emergent adverse events (TEAEs) reported during the study, and no subjects were withdrawn for safety reasons.

Table 1: Subject Demographics

- Number of subjects planned: 30 (100%), Number (%) of subjects in the Randomized population: 29 (96.7%), Number (%) of subjects in the Safety population: 26 (86.7%), Number (%) of subjects in the Evaluable population: 24 (80.0%), Number (%) of subjects with evaluable safety and/or efficacy data: 23 (76.7%), Withdrawn consent: 0 (0.0%).

Pharmacokinetics

- Mean plasma concentration-time curves for d-MPH for both OROS®-MPH and MPH-SR followed the expected temporal patterns that are characteristic for these formulations (Figure 3).

- p-value comparisons are presented in Table 4. 
- p-value = 0.0003.