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## Sensory Evaluation of Norvir® (Ritonavir) 100 mg Powder for Special Populations

John B. Morris<sup>1</sup>, David A. Tisi<sup>2</sup>, David Cheng Thiam Tan<sup>1</sup> and Jeffrey H. Worthington<sup>2</sup>

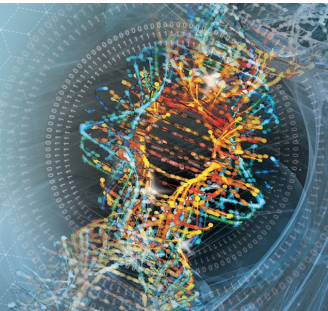
<sup>1</sup>AbbVie Inc., North Chicago, IL 60064, USA

<sup>2</sup>Senopsys LLC, Woburn, MA 01801, USA

CONTACT INFORMATION: John.B.Morris@abbvie.com; Tel.: +1-847-938-4996

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### PURPOSE

Norvir® (ritonavir) is an inhibitor of human immunodeficiency virus (HIV) protease and is indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection. Ritonavir is a BCS IV compound with poor solubility in water (~5 µg/mL) and limited oral bioavailability. Early stage development efforts were focused on an oral solution (OS) which provided reasonable bioavailability but exhibited taste-masking challenges and required the use of solvents (ethanol and propylene glycol) with potential pediatric toxicity. Norvir® oral powder, 100 mg (NOP) was developed to improve palatability and minimize or eliminate the use of solvents compared to the OS. The purpose of this study is to provide an overview of the development of NOP and determine the palatability of NOP and determine whether it is a suitable replacement for the OS for special populations including pediatrics.

### METHODS

NOP was developed using an amorphous solid dispersion (ASD) intermediate originally used for the Norvir® (ritonavir) 100 mg tablet. Though that adult formulation achieved the desired bioavailability and acceptable ambient chemical and physical stability, there remained a gap for pediatric patients and adults who are unable to swallow the tablets. NOP is manufactured by milling the ritonavir ASD extrudate intermediate and filling the resulting powder into sachets.

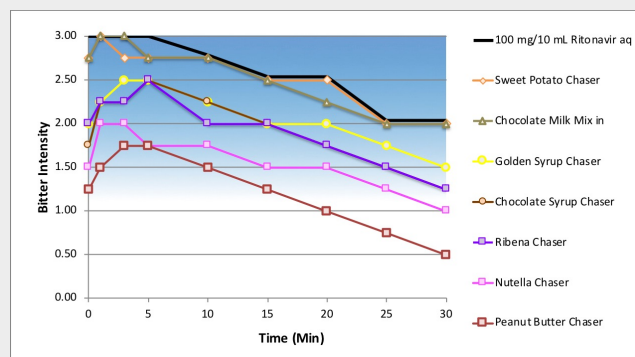


The dispersion of NOP produced a supersaturated aqueous solution of ritonavir drug substance that maintains the bioavailability achieved with OS. For sensory evaluation, NOP was suspended in water and administered with seven different soft food vehicles (either mixed-in or chased).

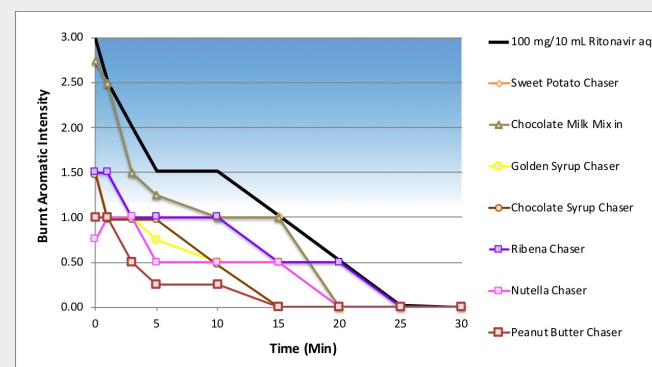
Samples were evaluated using the Flavor Profile Method of descriptive sensory analysis, an internationally recognized and approved open-source method. The Flavor Profile Method uses adult expert tasters trained on an established lexicon to measure sensory attributes (basic tastes, feeling factors, and aromatics) using a (0-3) intensity scale, calibrated with chemical reference standards. Sensory attributes above a slight intensity on the Flavor Profile scale (>1) are clearly perceptible to consumers/patients; this intensity is known as the recognition threshold. Therefore, for palatability, negative attributes (e.g., bitterness or irritation) should be below this threshold.

### RESULTS

100mg NOP dissolved in water was characterized by a strong intensity bitter basic taste that lingers at patient-perceptible intensities for more than 30 minutes in the aftertaste, and secondary aromatic off- notes described as "burnt" (polyethylene, wax, and hair). Administration of NOP with foods produced varied effects on bitterness reduction, ranging from < ½-unit (sweet potato chaser and chocolate milk mix-in) to a 1½-unit reduction in perception of bitterness with food chasers high in fat and/or sugar content with strong flavor intensity (peanut butter / Nutella).



The foods also had varied effects on the burnt aromatic off-notes of the NOP. All of the chasers produced greater reduction in the burnt aromatics than the chocolate milk mix-in (minimal reduction) with several at or below the threshold for perception ( $\leq 1$ ). The poor performance of chocolate milk may have been due to its administration as a mix-in, which would have allowed for an extended time for hydration, potentially releasing volatile aromatics.



During subsequent bioavailability studies, palatability of NOP in various beverages (water, infant formula, and chocolate milk) as well as admixed into a soft food (applesauce or vanilla pudding) was compared to that of the OS through study patient questionnaires. Only the NOP mixed in chocolate milk showed a modest improvement in overall palatability compared to the OS. The bioavailability study also demonstrated that administration of NOP with infant formula, chocolate milk, applesauce, or pudding was bioequivalent to administration in water.

### CONCLUSION(S)

The NOP formulation is an acceptable and age-appropriate dosage form to replace the OS for pediatric patients or patients who may have difficulties in swallowing a tablet. The majority of key design targets were achieved for the development program and suitable palatability assessments (Flavor Profile Method) were executed. While it was not feasible to substantially improve the palatability of the formulation itself, there may be widely available options for patients to reduce the lingering bitterness.

A variety of beverages and soft foods may be used as vehicles to administer NOP and/or consumed immediately as chasers after NOP dosing, offering patients more choices according to their individual taste preferences. Peanut butter, hazelnut chocolate spread, black currant, fruit drink concentrate, golden syrup, and chocolate syrup were shown to reduce the intensity and duration of the bitter aftertaste, most notably peanut butter and hazelnut chocolate spread.

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