Investigating the Structural Differences and Dynamic Relationship between Nirmatrelvir Solid Forms (Paxlovid™)

Authors: Maryam S. Sadeghi (1); Rui Guo (2); Michael A. Bellucci (3); Jaypee Quino (1); Erika L. Buckle (1); Matthew L. Nisbet (1); Zhuocen Yang (1); Danielle E. Gorka (1); Frank C. Pickard IV (5); Geoffery P. F. Wood (4); GuangXu Sun (3); Shuhao Wen (3); Joseph F. Krzyzaniak (1); Paul A. Meenan (1); Bruno Hancock (1); Chandler Greenwell (3) and Xiaojing Yang (1)
Presenting Author: Maryam S. Sadeghi
Affiliations: (1) Pfizer Worldwide R&D, Groton, Connecticut 06340, United States (2) Pfizer Worldwide R&D; Sandwich CT13 9ND, United Kingdom (3) XtalPi Inc.; Cambridge, Massachusetts 02142, United States (4) Former Pfizer employee now at Exscientia PLC 5. Former Pfizer employee now at Moderna
Corresponding Author's email: maryam.sadeghi@pfizer.com, xiaojing.yang@pfizer.com

Purpose
Two anhydrous polymorphs of the novel antiviral medicine nirmatrelvir were discovered during the development of Paxlovid™, Pfizer's oral Covid-19 treatment. A comprehensive experimental and computational approach was necessary to distinguish the two closely related polymorphs, herein identified as Forms 1 and 4.

Methods
Extensive experimental approaches were paired with computational methods, including powder X-ray diffraction (PXRD) and single-crystal X-ray diffraction (SXRD), slurry methods, thermal analysis, solid-state nuclear magnetic resonance (ssNMR) and Raman spectroscopy with computational investigations comprising crystal structure prediction (CSP), Gibbs free energy calculations, and molecular dynamics (MD) simulations of the polymorphic transition.

Results
Forms 1 and 4 were ultimately determined to be enantiotropically related polymorphs with Form 1 being the stable form above the transition temperature of ~ 17 °C. The work described in this paper shows the importance of using highly specialized orthogonal approaches to elucidate the subtle differences in structure and properties of similar solid-state forms. This synergistic approach allowed for unprecedented speed in bringing Paxlovid™ to patients in record time amidst the pandemic.

Conclusion
The case of nirmatrelvir reveals that the existing rules of thumb for distinguishing polymorphs are not always up to the task of distinguishing between real world polymorphs. Single crystal structures for both forms (Forms 1 and 4) were solved by Pfizer. The packing similarity analysis indicated Forms 1 and 4 were nearly isomorphous, prompting further investigation to address the challenge of differentiating the two forms. Ultimately, we were able to discern the subtle differences between Forms 1 and 4 only through the combined use of extensive experimental and computational approaches.

Keywords: Solid-state chemistry, Polymorphism, Transition dynamics, Computational chemistry, Molecular dynamics