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Deuterium Modification as a New Branch of Medicinal Chemistry to Develop Novel, Highly Differentiated Drugs

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Introduction

Concert Pharmaceuticals, a clinical stage biopharmaceutical company, uses deuterium to create and develop highly differentiated new medicines. This is a significant departure from the traditional use of deuterium modification as an analytical probe for metabolic studies. Concert uses its DCE Platform™ (Deuterium Chemical Entity) to develop new drugs that are designed to have first-in-class or best-in-class efficacy and/or safety. Deuterium modification provides a novel opportunity to develop new drugs by building upon existing scientific or clinical experience, potentially significantly reducing time, risk, and expense.

Concert's DCE Platform is based on the premise of the deuterium isotope effect wherein selective replacement of hydrogen atoms with deuterium creates more stable chemical bonds with carbon atoms. This modification can sometimes improve drug metabolism, increase half-life, or enhance bioavailability and exposure in a significant fashion. Deuterium is a safe, non-radioactive, naturally abundant isotope of hydrogen. The body of the average human adult already contains about 2 g of deuterium. Due to its similarity to hydrogen, deuterium modification usually has negligible effect on the intrinsic activity of a drug at its biological target. Concert's deuterium modification drug development approach is thus a powerful tool to improve the ADME (absorption, distribution, metabolism, and elimination) properties of a drug while maintaining its intrinsic biological activity. As many drugs under development or on the market suffer from sub-optimal pharmacokinetic and metabolic profiles, deuterium modification offers great promise to improve the profiles of these drugs and open opportunities for new uses.

Concert has advanced a number of deuterium-containing novel compounds designed to have unique therapeutic properties. The company has made preclinical and clinical progress with proprietary drug compounds in diverse therapeutic areas, including potential treatments for diabetic nephropathy, hot flashes, spasticity, neuropathic pain, and multiple myeloma.

CTP-499 for Diabetic Nephropathy

Concert's lead drug candidate is CTP-499, a novel potential treatment for diabetic nephropathy in type 2 diabetics. Diabetic nephropathy is the leading cause of end-stage renal disease, or kidney failure, and is expected to grow significantly as the incidence of type 2 diabetes increases rapidly. Despite the availability of blood pressure lowering agents, such as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), many patients continue to experience a decline in renal function and progress to kidney failure. As a result, there is a critical need for new drugs with untapped mechanisms that can further delay or prevent the decline of kidney function and eventual need for dialysis.

CTP-499 is an analog of 1-((*S*)-5-hydroxyhexyl)-3,7-dimethylxanthine (HDX), an active metabolite of Trental® (pentoxifylline), that Concert created by

replacing several key hydrogen atoms with deuterium. Trental, which is significantly metabolized to HDX, is approved in the US for the treatment of intermittent claudication and has been reported in preliminary studies to have beneficial effects on urinary albumin excretion and renal function decline. Based on the pharmacology and degree of exposure, it appears these renoprotective effects may be due in large part to HDX. CTP-499 and HDX have similar physical, chemical, and pharmacological properties; however, Phase I clinical data with CTP-499 shows that incorporation of deuterium leads to increased exposure to the species responsible for the renoprotective effects.

To date, four Phase I studies have been completed with CTP-499. One study showed that controlled-release (CR) formulations of CTP-499 form the same metabolites as Trental; however, exposure to species possessing beneficial anti-inflammatory, anti-fibrotic, and immunomodulatory effects was increased with CTP-499 relative to Trental administration. The overall pharmacokinetic profile suggested CR CTP-499 may be suitable for once-daily dosing. A second study, which tested single ascending doses of CR CTP-499, showed that doses up to and including 1800 mg were well tolerated. Based on these results, CTP-499 shows unique potential as a treatment for diabetic nephropathy, along with reduced development risk given the abundant safety experience with Trental.

In early 2012, Concert initiated a 6-month Phase II efficacy study of CTP-499 in diabetic patients with mild-to-moderate renal impairment who are at particular risk of disease progression due to macroalbuminuria (excessive amounts of albumin in their urine). The primary goal of the study is to investigate the effect of CTP-499 on a measure of disease progression, urinary albumin excretion, with secondary goals related to safety/tolerability and effects on renal function and various biomarkers.

The impact of deuterium on cost of goods varies depending on the drug. Concert invested in process development research that resulted in an elegant, highly efficient manufacturing process for CTP-499 active pharmaceutical ingredient (API). The synthesis has been designed to use the most cost-effective deuterated starting material and produces API in > 70% yield. Because CTP-499 is a single enantiomer, the desired enantiomer is directly isolated using an asymmetric synthesis with high enantioselectivity and little loss of deuterium. Finally, Concert creatively implemented recycling and recovery techniques through which > 90% of the deuterium used is either incorporated into the API or recovered for future use. CTP-499 is manufactured on a scale of hundreds of kilograms and is expected to have a cost of goods that is competitive with other commercial APIs.

CTP-347: Deuterium Modification of Paroxetine

Concert's first clinical candidate was CTP-347, a selectively deuterated analogue of paroxetine. CTP-347 was designed to eliminate the irreversible inhibition of a key metabolizing enzyme (CYP2D6) caused by a highly reactive paroxetine metabolite that covalently binds to the enzyme. In certain patients potentially benefiting from therapy with paroxetine who also receive endocrine disrupting agents, such as post-menopausal women and cancer patients, paroxetine use can be complicated or contraindicated as it causes extensive drug-drug interactions (DDIs) with other medications. In vitro metabolism experiments with CTP-347 demonstrated little to no CYP2D6 inactivation, as a result of deuterium-based metabolic shunting, which essentially prevented the formation of the reactive metabolite. Other studies showed the intrinsic pharmacology of paroxetine was unchanged after deuterium incorporation. A 96-subject single and multiple ascending dose clinical study with CTP-347 provided further evidence, consistent with the in vitro data, that irreversible inactivation of the CYP2D6 enzyme did not occur with CTP-347. This clinical study with CTP-347 represents the first clinical demonstration that deuteration can be utilized to avoid the formation of undesired metabolites in humans.

CTP-354: A Deuterium-Modified Subtype-Selective $GABA_A$ Modulator

Concert has created deuterated subtype-selective $GABA_A$ modulators that represent a promising therapeutic modality for the treatment of spasticity and chronic pain, with the potential for improvement over existing first-line therapies. A subtype-selective $GABA_A$ modulator has the potential to address a major unmet need by retaining desirable therapeutic aspects of the benzodiazepines - anxiolytic and spasmolytic activity - while minimizing the sedative and tolerance effects.

Concert's $GABA_A$ modulator program is based upon agents that have been profiled in multiple preclinical efficacy models, representing an opportunity to leverage extensive therapeutic data to advance a clinical candidate. Concert's $GABA_A$ modulator lead compound, CTP-354, is a deuterated version of a preclinical agent discovered at Merck. The Merck compound, L-838417, was targeted by Concert for deuterium substitution because its promising pharmacology was extensively characterized in the literature, although it possessed poor pharmacokinetic profiles in preclinical species and was never progressed into clinical development. L-838417 was shown to have desirable $GABA_A$ subtype selectivity in vitro: no agonist activity at the *alpha*-1 subtype but partial agonism activities at the *alpha*-2,

alpha-3, and *alpha*-5 subtypes. This in vitro subtype profile for L-838417 positively translated to its in vivo pharmacology profile, with demonstrated preclinical efficacy in anxiety, muscle relaxation, inflammatory pain, and neuropathic pain, and significantly reduced sedation and ataxia liabilities in rodents and primates.

Deuterated CTP-354 demonstrated substantial pharmacokinetic improvement compared to L-838417 in rats and dogs, and has recapitulated beneficial L-838417 pharmacology in both in vitro and in vivo studies. The Chung model, a sciatic nerve ligation model of neuropathic pain, was performed in the rat to compare oral doses of CTP-354 first to L-838417, and then to the standard of care, gabapentin. CTP-354 was efficacious in both studies with a prolonged pharmacodynamic effect versus L-838417, which correlated with the higher CTP-354 plasma level observed at the final timepoint. In the comparison of CTP-354 to gabapentin, CTP-354 demonstrated an excellent dose response and showed equivalent efficacy to gabapentin at similar doses. At the doses used in these studies, CTP-354 was well tolerated in a rat rotarod study assessing potential for sedation and ataxia. The excellent pharmacokinetic and pharmacology profiles of CTP-354 support the potential use as a non-sedating treatment of spasticity and neuropathic pain.

C-21359: A Deuterium-Stabilized Enantiomer of Lenalidomide

Concert has developed C-21359 as a novel deuterated enantiomer of racemic lenalidomide (Revlimid®), an oncology agent indicated for use in multiple myeloma and in myelodysplastic syndromes (MDS). Revlimid contains a mixture of *R* and *S* enantiomers that interconvert in vivo. While the *S* enantiomer appears to possess the beneficial activities associated with Revlimid, dosing of the single *S* enantiomer is not considered useful, as it would rapidly convert in vivo to the *R/S* mixture. Concert has discovered a specific deuterium modification pattern that optimally slows the interconversion of enantiomers, thus enabling administration of the more beneficial *S* enantiomer with minimal exposure to the *R* enantiomer.

C-21359 demonstrates enhanced activity versus Revlimid in immunomodulatory and anti-cancer in vitro efficacy assays. Deuterium-stabilized, single *S*-enantiomer dosing drives this improvement in pharmacological efficacy, as deuterated racemic lenalidomide derivatives show no improvement over Revlimid in these assays. C-21359 is expected to be useful for the treatment of multiple forms of cancer and myelodysplastic syndrome, with the potential to expand into non-cancer indications.

Summary

The aforementioned examples show that deuterium modification may be used broadly to improve upon previously known compounds or their analogs, in turn offering potential benefits in a wide range of therapeutic areas. It should be noted, however, that deuterium effects on the overall metabolism of a drug are not predictable *a priori*. For example, deuterium substitution may have no observable effect, or may cause metabolism to shift preferentially to another existing pathway. In select cases, Concert's deuterium modifications can impart significant improvements to the metabolic properties of a drug. Thus far, this relatively new approach to medicinal chemistry has yielded a number of promising drug candidates with differentiated therapeutic properties. ■

Dr. Philip Graham

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Dr. Philip Graham currently serves as Vice President of Program Development at Concert Pharmaceuticals. He has more than 20 years experience in the pharmaceutical and biotechnology industry. Prior to joining Concert, Dr. Graham was Vice President of Product Management and Imaging at EPIX Pharmaceuticals, where he also had management responsibility for chemical and analytical development along with pharmacology and toxicology. Before joining EPIX, Dr. Graham worked at Eli Lilly and Co. for more than 5 years in analytical development. He earned his BS with honors from the University of Otago, New Zealand, and his PhD in Analytical Chemistry from the University of Massachusetts, Amherst.

Dr. Julie Fields Liu

Director, Research Management, Concert Pharmaceuticals

Dr. Julie Fields Liu is currently Director, Research Management at Concert Pharmaceuticals, where she serves as a Program Team Leader, Intellectual Property/Research Liaison, and Manager of a multi-year outsourced chemistry collaboration. She is a medicinal chemist and has 12 years of experience in the pharmaceutical and biotechnology fields. Prior to joining Concert as one of the first 10 employees, Dr. Liu worked at Millennium Pharmaceuticals in the areas of oncology, inflammation, and metabolic disease. She earned her BS in Chemistry with honors and distinction from the University of North Carolina at Chapel Hill, and her PhD in Organic Chemistry from the University of California, Berkeley.

David Turnquist

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David Turnquist currently serves as Director of Analytical Chemistry at Concert Pharmaceuticals. He has more than 14 years of experience in the pharmaceutical industry. Prior to joining Concert, Mr. Turnquist worked at Vertex Pharmaceuticals and Merck Research Laboratories serving in a variety of disciplines from Physical and Analytical Chemistry to Analytical Development to CMC Project Management. He earned his BS in Biology and Chemistry from the University of North Carolina at Chapel Hill and his MBA from Boston College.