March 10, 2014

WELLS FARGO SECURITIES

# *Equity Research*

## Concert Pharmaceuticals, Inc.

**CNCE: We Initiated Coverage With An Outperform Rating**

**Outperform / V**

Sector: Biotechnology
Market Weight

***Initiation of Coverage***

- **Summary:** We initiated coverage of Concert Pharmaceuticals with an Outperform rating and a $21-23 valuation range. We believe both CTP-354 and CTP-499 have the potential to address broad markets where there remains a need for better tolerated and/or more effective agents, and see multiple long-term shots on goal for CNCE with a high aggregate revenue opportunity (about $700 million by 2023E) should CNCE's proprietary and partnered candidates be successful. We also believe CNCE's deuteration chemistry platform provides a solid long-term foundation for the continued production of differentiated pipeline products. Overall we believe this promise is underappreciated; our valuation range is based on a blend of probability-adjusted, discounted out-year EPS and sales multiples.
- **Lead candidate CTP-354, in our view, has considerable long-term potential as a selective, non-sedating benzodiazepine-like drug for muscle spasticity and other neuropsychiatric indications.** Benzos are a mainstay of treatment for many disorders, but are limited by side effects. Although '354 is early stage and activity needs to be tested in patients, initial pharmacokinetic data looked solid and a receptor occupancy study helps support the potential for a broader therapeutic window than existing therapies, a characteristic we believe would be embraced in the market.
- **CTP-499 has shown promising signals in diabetic kidney disease, an area in which we foresee a large future opportunity if the drug is successful.** Though the phase II missed its primary endpoint, we believe there were signals suggestive of activity that warrant exploring moving the drug into pivotal studies with a partner; should '499 ultimately be approved, we believe $1B+ in long-term end-user sales would be very achievable.
- **Partnerships provide key validation for CNCE's approach and the possibility of meaningful long-term milestone/royalty revenue.** CNCE has partnerships with CELG, JAZZ, and AVNR on deuterated drugs. While these candidates are generally early, if deuteration meaningfully enhances dosing and/or PK, we believe each candidate could capture significant long-term market share. We believe these partnerships strongly validate CNCE's platform, and the Food and Drug Administration's (FDA) amenability to an expedited path for AVNR reflects regulatory comfort with deuteration that could bode well for CNCE's future programs.
- **We see significant value in the company's deuteration chemistry platform.** Deuteration can potentially improve PK/metabolism of drugs without affecting pharmacology, and we believe CNCE has established itself as the leader in analyzing where selective deuterium substitution of compounds could provide meaningful clinical benefits. We believe this provides a strong foundation for long-term pipeline sustainability and additional partnerships.

**Valuation Range: $21.00 to $23.00** from NA to NA
Our valuation range is based on applying a 30x multiple to our 2022 estimated EPS and discounting at 15%, blended with 2.5x multiple of 2022 estimated sales, and discounting 12%. Key risks, in our view, are failure of '354 and/or '499 to show efficacy in subsequent studies and regulatory hurdles in spasticity or CKD.

**Investment Thesis:**
We believe Concert's proprietary and partnered candidates, and drug deuteration platform, will generate long-term value.

| | 2013A | 2014E | | 2015E | |
|---|---|---|---|---|---|
| **EPS** | | **Curr.** | **Prior** | **Curr.** | **Prior** |
| **Q1** (Mar.) | NE | ($0.64) | NE | NE | NC |
| **Q2** (June) | NE | (0.41) | NE | NE | NC |
| **Q3** (Sep.) | NE | (0.52) | NE | NE | NC |
| **Q4** (Dec.) | NE | (0.52) | NE | NE | NC |
| **FY** | NE | $2.05 | NE | ($2.05) | NE |
| **CY** | NE | $2.05 | | ($2.05) | |
| **FY P/E** | NM | 7.3x | | NM | |
| **Rev.(MM)** | NE | $3,520 | | $22,520 | |

*Source: Company Data, Wells Fargo Securities, LLC estimates, and Reuters*
*NA = Not Available, NC = No Change, NE = No Estimate, NM = Not Meaningful*
*V = Volatile, = Company is on the Priority Stock List*

| | |
|---|---|
| Ticker | CNCE |
| Price (03/07/2014) | $14.88 |
| 52-Week Range: | $12-17 |
| Shares Outstanding: (MM) | 0.0 |
| Market Cap.: (MM) | $0.0 |
| S&P 500: | 1,878.04 |
| Avg. Daily Vol.: | 0 |
| Dividend/Yield: | $0.00/0.0% |
| LT Debt: (MM) | $0.0 |
| LT Debt/Total Cap.: | 0.0% |
| ROE: | NM |
| 3-5 Yr. Est. Growth Rate: | NE |
| CY 2014 Est. P/E-to-Growth: | NM |
| Last Reporting Date: | 12/31/2013 |

*Source: Company Data, Wells Fargo Securities, LLC estimates, and Reuters*

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**Please see page 29 for rating definitions, important disclosures and required analyst certifications**
**All estimates/forecasts are as of 03/10/14 unless otherwise stated.**

## Company Description

Concert Pharmaceuticals (CNCE), Inc., headquartered in Lexington, Massachusetts, is a biotechnology company focused on improving therapies in a variety of areas such as neurology and kidney disease, using its platform technology around deuterium substitution. The company's lead development candidate is CTP-354, a GABA-A partial agonist in development for muscle spasticity. Another development candidate is CTP-499, a phosphodiesterase enzyme inhibitor in development for diabetic kidney disease. Alongside '354 and '499, its partnered pipeline includes CTP-730, a deuterated anti-inflammatory drug partnered with Celgene, AVP-786 for major depressive disorder partnered with Avanir, and JZP-386, a deuterated version of Xyrem for narcolepsy, partnered with Jazz.

## Investment Thesis

**We have initiated coverage of CNCE with an Outperform rating and a $21-23 valuation range.** We believe both CTP-354 and CTP-499 have the potential to address broad markets where there remains a need for better tolerated and/or more effective agents, and see multiple long-term shots on goal for CNCE with a high aggregate revenue opportunity (approximately $700 million by 2023E) should the company's proprietary and partnered candidates be successful. We also believe the company's deuteration chemistry platform provides a solid long-term foundation for the continued production of differentiated pipeline products. In our view, CNCE shares undervalue the prospects of the company's programs and the potential of its deuteration chemistry platform.

**We believe lead drug CTP-354, as a potentially non-sedating benzodiazepine-like drug, could have considerable long-term potential in muscle spasticity and a number of other indications.** Benzodiazepines have long been a mainstay of treatment of neuropsychiatric disorders including muscle spasticity, anxiety, and pain, but are significantly limited by side effects such as sedation and dizziness. Availability of more selective modulators of the GABAA receptor, which dial out such adverse events while maintaining clinical activity, would represent a significant advance, in our view, but efforts to develop drugs with such a profile have not been successful to date. CNCE's CTP-354 is a deuterated version of an agent that had shown desirable selectivity, but whose poor PK properties had prevented it from progressing into human studies. Animal models corroborated that deuteration indeed dramatically improved exposure, and '354 showed favorable, dose-dependent PK in a single-dose human study. Though the activity of '354 has not yet been tested in patients, a receptor occupancy study conducted by the company in healthy volunteers demonstrated that the agent binds to $GABA_A$ receptors far more than currently available benzodiazepines would at their therapeutic doses, and at doses having minimal side effects, helping support the potential differentiation of CNCE's approach and the idea that '354 may have a window at which benefits but no benzo-like AEs are observed. We believe this helps improve the agent's risk profile despite its early stage. We believe data in H2 2014 from the ongoing multiple ascending dose (MAD) study will help confirm that the steady-state therapeutic window remains wide and could provide a near-term catalyst by further de-risking the program. Ultimately, should the agent demonstrate success in spasticity, the first indication CNCE is pursuing, we believe the market would embrace a less-sedating, once-daily agent and foresee more than $300 million in potential sales (with relatively modest required commercial investment). Longer term, should the profile live up to its potential, we believe '354 could address needs in much larger markets, like anxiety and pain.

**We believe CTP-499 has shown some promising signals in diabetic kidney disease, an area where there could be a large future opportunity.** '499, a wholly owned deuterated metabolite of pentoxifyllene, a phosphodiesterase inhibitor, recently completed a phase II study in diabetic nephropathy. Though the trial did not meet its primary endpoint of improving proteinuria relative to placebo at 24 weeks, longer term data showed signals of benefits on renal function. Additional data such as biomarker results, expected to be presented H1 2014, will likely be important to help better elucidate the mechanism and whether such treatment effects are real. Still, the fact that approved agents for kidney disease have shown similar patterns of benefits taking longer to emerge, and the greater regulatory importance of long-term protection against significant renal function declines–which '499 appeared to demonstrate–do suggest true activity for the drug and could support a path forward. Following final analysis of the study data, CNCE plans to meet with FDA mid-year to discuss future plans, and subsequently out-license the drug to a potential partner. We believe full analysis of the data and clarity on the regulatory path will be important to prompt a partner to make the considerable phase III and commercial investment needed to bring the drug to the market. If ultimately successful, though, we believe the market opportunity would be very significant for a drug with a novel mechanism in the large addressable CKD population, potentially $1 billion or greater, and generating more than $150 million annually in long-term royalties to CNCE without the need for any additional expenditure on the program.

**CNCE's partnerships provide key industry and regulatory validation of their approach, in our view, and could produce meaningful long-term milestone and royalty revenue for the company.** CNCE has partnerships with Celgene, Jazz, and Avanir for deuterated versions of each of these companies' respective compounds, which have the potential for having dosing and safety advantages over predecessor compounds, opening up expanded or new markets, and prolonging lifecycle. Though the structure of each deal differs, in general for these programs, CNCE has limited costs beyond phase I, the potential for up to $1.6 billion in future milestone payments, and the potential for royalties on future sales. In particular, for a longer acting version of Jazz's Xyrem, a narcolepsy drug expected to sell $1.3 billion annually, but which currently requires middle of the night dosing, we believe the sales and royalty opportunity could be considerable. Beyond potential financial benefits, we believe Celgene's up-front payment and interest in purchasing equity provide strong external validation of the company's deuterium chemistry platform, and that FDA's permitting Avanir to move rapidly into phase II referencing data from the predecessor compound reflects well on regulatory comfort for the deuteration concept and the possibility other programs could have expedited development paths.

**We see significant value in the company's deuteration chemistry platform, which we believe could provide a fertile foundation for long-term pipeline sustainability.** Deuterium is a naturally occurring isotope of hydrogen, which, when incorporated into compounds selectively, can alter PK and metabolism without influencing pharmacology. As such, deuterium can potentially improve administration/convenience of existing compounds; enable development of compounds with interesting properties, but which without deuteration lacked sufficient drug-like properties; and enhance a drug's safety profile. Though the idea of deuteration is not new, we believe CNCE's years of developing analytical chemistry and tools to understand exactly which chemical modifications will confer clinically meaningful improvements has made it the leader in the field. We believe this concept of "non-obviousness" fostered by CNCE's expertise also helps confer patentability of its drugs. CNCE has already synthesized numerous deuterated compounds and moved several into the clinic, a trend we expect to continue and to provide a sustainable stream of assets for the company to explore over the long term. We also believe that as preclinical and clinical studies continue to validate the concept and prove the deuteration technology can have practical applications, CNCE will attract additional partnerships, helping expand the number of shots on goal and provide non-dilutive funding.

## Valuation

**We have established a $21-23 valuation range for Concert.** We base our valuation analysis on our probability-adjusted revenue and EPS projections for the company's key proprietary and partnered products, CTP-354 in spasticity and anxiety, CTP-499 for diabetic kidney disease, AVP-786 for major depressive disorder, and JZP-386 for narcolepsy. We assume a 25% probability of success for CTP-354 in spasticity and a 10% probability of success in anxiety; for CTP-499, we assume a 20% probability of success, and assume that the drug is commercialized by a partner, with Concert receiving royalties on sales. For the partnered programs, we assume 10-15% probabilities of success for AVP-786 given the program's new mechanistic approach and JZP-386, given its early stage. Assuming approximately 24.7 million shares diluted shares outstanding, which accounts for at least one potentially dilutive capital raise (assuming up-front payments for a worldwide '499 partnership and EU '354 partnership, and non-dilutive financing from milestones for currently partnered programs along the way), we arrived at a probability-adjusted 2022 EPS of $1.91. Applying a 30x multiple, which we believe is appropriate for a biotechnology company of Concert's size and potential, and discounting at 15% for approximately seven years, would yield a valuation of $19. Using a valuation analysis based on sales multiples, applying a 6x multiple on our estimated probability-adjusted worldwide product sales of $243 million, and discounting back approximately seven years at 12% yields a potential valuation of $24. Blending these two methodologies would yield a valuation range of $21-23. We believe this range adequately captures the potential considerable potential upside opportunities for the company's proprietary and partnered programs, while accounting for the inherent risks given stage of development and data to date.

**Exhibit 1. Valuation Analysis**

| Year: | 2022E | Discount (yrs) | 7.8 | EPS: | $9.80 | Shares out: | 24,734 | |
|---|---|---|---|---|---|---|---|---|
| Product: | Indication: | Region | Probability of success: | Sales | Net to company: | EPS contribution | Probability-weighted EPS contribution: | Probability-weighted sales |
| CTP-354 | Spasticity | Worldwide | 25% | $222M | 46% | $4.07 | $1.02 | $101M |
| CTP-354 | Anxiety | Worldwide | 10% | $84M | 46% | $1.55 | $0.16 | $38M |
| CTP-499 | Diabetic CKD | Worldwide | 20% | $713M | 10% | $2.88 | $0.58 | $71M |
| AVP-786 | Depression | Worldwide | 10% | $158M | 10% | $0.64 | $0.06 | $16M |
| JZP-386 | Narcolepsy | Worldwide | 15% | $165M | 10% | $0.67 | $0.10 | $16M |
| Total | | | | $1,342M | | $9.82 | $1.91 | $243M |

| | Discount Rate: | | | | |
|---|---|---|---|---|---|
| EPS Multiple: | 5% | 10% | 15% | 20% | 25% |
| 15 | $20 | $14 | $10 | $7 | $5 |
| 20 | $26 | $18 | $13 | $9 | $7 |
| 25 | $33 | $23 | $16 | $11 | $8 |
| 30 | $39 | $27 | $19 | $14 | $10 |
| 35 | $46 | $32 | $22 | $16 | $12 |
| 40 | $52 | $36 | $26 | $18 | $13 |

| | Discount Rate: | | | | |
|---|---|---|---|---|---|
| Sales Multiple: | 10% | 11% | 12% | 13% | 14% |
| 5 | $23 | $22 | $20 | $19 | $18 |
| 6 | $28 | $26 | $24 | $23 | $21 |
| 7 | $33 | $30 | $28 | $26 | $25 |

Source: Wells Fargo Securities, LLC estimates

## Upcoming Milestones and Product Pipeline

**Exhibit 2. Upcoming milestones**

| Product | Event | Timeline |
|---|---|---|
| CTP-354 | Data from MAD study, occupancy study | 2H14 |
| | Initiate ph.II trials in MS/SCI spasticity patients | 2H14 |
| | Report ph.II spasticity results | end-2015/early-2016 |
| | Potentially initiate ph.III program | mid-2016 |
| CPT-499 | Present full 48wk data from ph.II, including biomarkers | 1H14 |
| | End-of-ph.II meeting with FDA | mid-2014 |
| | Sign partnership agreement | 2H14+ |
| AVP-786 | Ph.II for treatment-resistant MDD initiation | 2H14 |
| CTP-730 | Ph.I study initiation | 2H14 |
| JZP-386 | Ph.I study initiation | 2014 |

Source: Company reports and Wells Fargo Securities, LLC estimates

**Exhibit 3. Product pipeline**

| Product (partner) | Indication/mechanism | Status |
|---|---|---|
| CTP-354 | Spasticity, anxiety, pain; subtype selective GABAa receptor modulator | Phase I |
| CTP-499 | Diabetic nephropathy; multi-subtype selective inhibitor of phosphodiesterases | Phase II |
| AVP-786 (AVNR) | Neurologic and psychiatric disorders, depresion; deuterium-substituted dextromethorphan analog plus low-dose quinidine | Entering phase II |
| CTP-730 (CELG) | Inflammatory diseases | Entering phase I |
| JZP-386 (JZP) | Narcolepsy; deuterium-substituted Xyrem analog | Entering phase I |
| C-10068 | Pain and seizures; deuterium-substituted dextromethorphan/ analog | Preclinical |
| d-ivacaftor | CF, COPD | Preclinical |
| d-praziquantel (NIH) | Parasitic diseases | Preclinical |

Source: Company reports and Wells Fargo Securities, LLC

## Key Risks

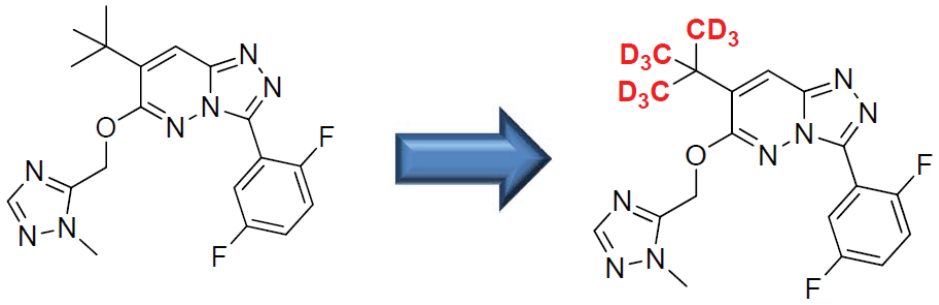
- **Clinical risk.** Lead product CTP-354 is in early-stage development and has not been advanced into proof-of-concept studies as of yet. While receptor occupancy studies show the drug may be reaching its target, it is possible studies in patients with spasticity may not show effects or demonstrate a wide enough therapeutic window to support clinical differentiation or movement into future studies in spasticity, anxiety, or pain. It is also possible safety signals (QTc changes were observed in the phase I, but were not deemed clinically relevant) could emerge in longer, larger studies, as the clinical exposure to date has been limited, which could delay or halt future development or compromise the agent's long-term opportunity. CTP-499 showed signals of potential activity in CKD, but kidney disease has historically been a difficult indication to develop drugs for, and data in the phase II proof-of-concept study were mixed. Partnered programs remain early stage, adding risk as to whether they ultimately succeed.
- **Regulatory risk.** CTP-354 is on partial clinical hold, and while CNCE's modeling predicts that doses needed for adequate receptor occupancy to treat spasticity should be achievable with allowable tested doses, if higher doses are required for other indications (or appear to be needed for spasticity) and CNCE's preclinical work is not sufficient for the FDA to remove this restriction on dose escalation, it could limit the ultimate opportunity. Regulatory views on endpoints in spasticity may be evolving, and it will likely be important for the future phase III development program to conform to most current FDA requirements; the endpoint used at present, Ashworth score, can be somewhat unreliable and requires careful study conduct, adding risk to the drug demonstrating efficacy, in our view. The regulatory safety bar for broader market indications such as anxiety and pain is likely to be high, so tolerability and the AE profile will likely need to be very clean in order for CNCE to be able to capture these potential opportunities. For potential new CKD drugs like CTP-499, the regulatory path in the United States is not completely well established. While we believe protection from major creatinine worsening could be part of a future registrational endpoint, any need for additional long-term outcomes could require a larger, longer phase III program, potentially adding costs and dissuading a potential partner.
- **Commercial risk.** There are several other drugs on the market for spasticity, anxiety, and pain, many of which are generic, which could potentially compete with '354. As such, we believe it will be important not only for '354 to demonstrate clear differentiation such as on dosing frequency and tolerability profile, but for CNCE to build a sales force that effectively communicates those attributes to enable successful physician adoption and payer amenability. '499 would likely need to be commercialized by a larger company with an existing sales infrastructure; as such, CNCE would need to find a collaborator interested in investing in the phase III and commercialization costs for the drug even with the somewhat mixed data and on favorable terms to CNCE.
- **Financial risk.** CNCE's candidates are generally at an early stage of development, and while the company should be able to generate some meaningful non-dilutive cash from existing and future partnerships, this will likely rely on the clinical successes of their programs, and CNCE may require additional funding as '354 advances in the clinic. Raising cash in the equity market could result in dilution to shareholders.

## Developmental Programs

### CTP-354

**Overview. CTP-354 is a subtype selective GABA modulator in phase I development for spasticity.** The compound is a deuterated version of L-838,417, a compound MRK developed several years ago to be a non-sedating anxiolytic, but which was not advanced into the clinic, due to poor pharmacokinetics. CNCE completed a phase I single ascending dose study and GABA receptor occupancy study, and is testing the agent in a multiple ascending dose study in healthy volunteers, with data by H2 2014.

**Exhibit 4. Chemical structure of CTP-354, relative to its undeuterated predecessor compound**

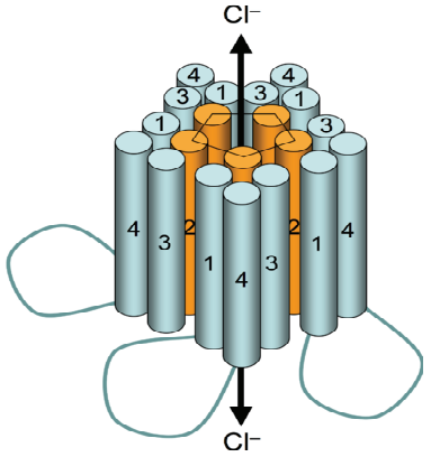



**L-838,417** **CTP-354**

Source for both images: Liu, et al, 2012, American College of Neuropsychopharmacology

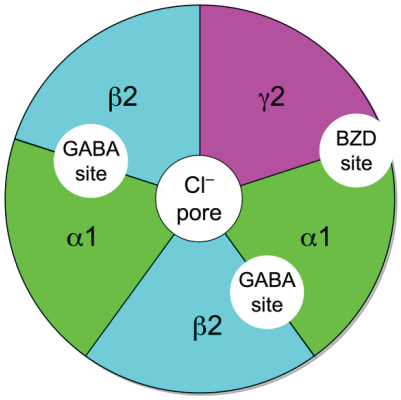
**Improving selectivity to GABA subtypes has the potential to meaningfully reduce sedation and other side effects, which would be a major advance in the treatment of many neuropsychiatric disorders.** The $GABA_A$ receptor is a ligand-gated chloride channel that inhibits neurotransmission in the central nervous system. The $GABA_A$ receptor itself is a pentameric protein with subtypes composed of α, β, and γ gamma subunits. Mutational studies based on gene knocking in mice have demonstrated that the sedative, ataxic, and dependence effects of benzodiazepines are mediated by the α1 subtype. In contrast, agonist activity at the α2 and α3 subtypes is thought to be associated with anxiolytic, analgesic, and spasmolytic activities. α5 subtype activity is associated with cognitive effects. Benzodiazepines on the market today activate $GABA_A$ in a non-selective manner, binding to $GABA_A$ at the interface of a gamma subunit and either an α1, α2, α3, or α5 subunit; dialing out α1 activity would theoretically retain the desired efficacy profile, while reducing side effects.

**Exhibit 5. $GABA_A$ schematic demonstrating five subunits arranged around Cl- conduction pore**




Source: Wikipedia, company reports and Wells Fargo Securities, LLC

**Exhibit 6. CNS $GABA_A$ typically comprises two α subunits, two β units, and a γ subunit**




Source: Wikipedia, company reports, and Wells Fargo Securities, LLC

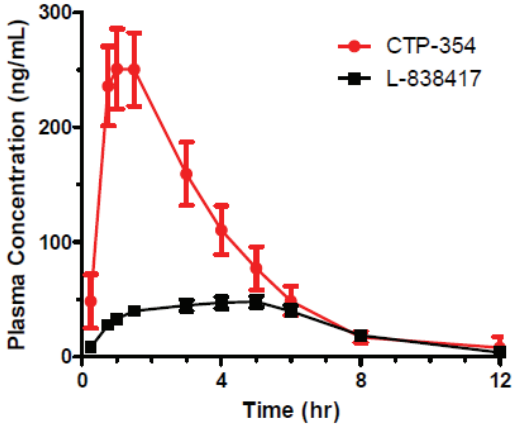
Indeed, the predecessor compound '417, in animal models, demonstrated potent anxiolytic activity, but was not sedating.

**Preclinical Studies**

**Preclinical data suggest '354 addressed the PK issues with predecessor compound '417, while maintaining '417's favorable partial agonist activity:**

- **In rat models, the first primary benefit of deuteration noted was an increase in metabolic stability.** Deuterated '354 was demonstrated to increase drug exposure by 3-5x with much higher peak plasma concentrations post oral administration. The increase in drug exposure came from an increase in the $C_{max}$ of '354, more so than from an extended half-life compared to '417 (possibly because in animals, unlike in humans, there are two dominant paths for metabolism instead of one, indicating that in humans, the half-life could still be meaningfully improved, as well). Specifically, in an oral discrete dosing study in rats (n = 8, 1mg/kg), the mean $C_{max}$ (ng/mL) was 261, versus 55, or a 4.7x increase, while mean $t_{1/2}$ was 1.76 hours, versus 1.74 hours, in '354 and '417, respectively. This translated into a relative increased drug exposure of 2.9x as represented by the average calculated area under the curve (AUC) of 1,007, versus 347 in '354 and '417, respectively.

**Exhibit 7. PK profiles in the rat after oral administration of '354 and '417 demonstrate relative increased exposure of '354**



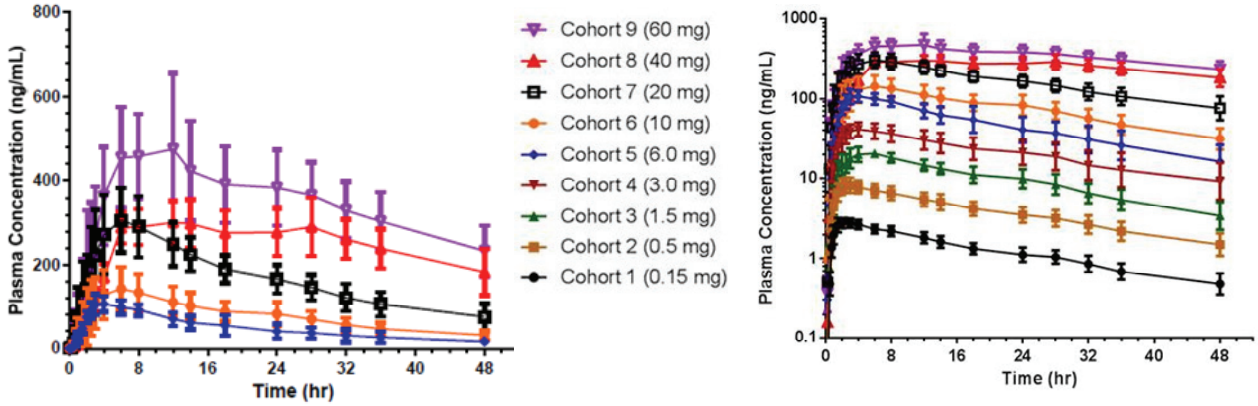

Source: Liu, et al, 2012, American College of Neuropsychopharmacology

- **The PK parameters of '354 and '417 were also compared in an oral dosing study in male dogs (n=4, crossover study, 15mg/kg), where advantages were also observed.** While the sample size was small, again deuteration appeared to improve the pharmacokinetic properties of the molecule. Mean $C_{max}$ increased to 2,587 ng/mL versus 492 ng/mL – a 5.3x increase; mean half-life increased by 1.3-fold. Overall, the relative increased drug exposure was calculated to be 4.5x, as represented by an average AUC of 10,882 versus 2,410 in '354 and '417, respectively.
- **'354 also showed longer lasting activity in the Chung rat pain model versus gabapentin, which is indicative of its efficacy in *in vivo* animal models.** The Chung rat is a model for neuropathic pain via ligation of the sciatic nerve. Initially, '354 and '417 were compared with oral dosing up to 10 mg/kg, and then up to 100mg/kg versus gabapentin at 100 mg/kg as a follow-up positive control. In the initial study at 10 mg/kg dosing, '354 was found to be efficacious, demonstrating sustained blood levels and statistically significant prolonged pharmacodynamic effect versus '417. On follow-up, '354 demonstrated a dose response and efficacy equivalent to standard-of-care gabapentin with a longer duration of effect, with efficacy lasting to six hours.
- **Evidence of selectivity in animal models was also seen.** The rat rotarod model was used to evaluate sedation/ataxia liability via latency to fall from rod, using dosing up to 100 mg/kg that matched levels used in the efficacy studies. '354 was found to be well tolerated, with no sedative/ataxic effects on rat rotarod performance (n=4) compared to three positive controls dosed with psychotropic medications including a barbiturate and benzodiazepine. '354's tolerability may serve as further proof of its selectivity for $GABA_A$ α2 and α3 subtypes.

**Clinical Data**

**The drug showed favorable PK with once-daily potential in a single ascending dose (SAD) phase Ia study in healthy volunteers.** Concert conducted an SAD study in 71 healthy volunteers, in which eight cohorts of six active and two placebo subjects each (and one cohort of seven subjects), were randomized to receive single doses of 0.15mg, up to 60mg of '354 or placebo. The increase in $t_{1/2}$ compared to what might be expected from the predecessor compound was substantial: 12 hours at the lowest dose and up to 30 hours at the highest, proving the concept that deuteration significantly enhances PK. The drug also showed smooth, dose-dependent exposure, as demonstrated in Exhibit 8.

**Exhibit 8. Phase Ia cohorts 5-9, mean plasma concentration versus time, in absolute and logarithmic scale**




Source for both graphs: Company reports and Wells Fargo Securities, LLC (used with company permission)

**Tolerability was reasonable, suggesting CNCE could potentially find a window in which benefits are conferred, but α1 related sedation does not take hold.** There were no SAEs in the study and the study was completed at 60mg, due to receptor occupancy saturation rather than reaching a maximum tolerated dose (MTD). $GABA_A$ related side effects did occur in what looked to be a dose-dependent manner, with side-effect-like dizziness and somnolence seen at 20mg and higher, and nausea/vomiting at 60mg; however, only at 40mg and 60mg were anything more than mild AEs observed. This side-effect profile was similar to observations in the company's receptor occupancy study (discussed in more detail further on). Indeed, our investigator feedback indicated that despite some dizziness at higher dozes, 20-40mg were very well tolerated, and side effects could potentially be further managed through titration.

Timing-wise, many of these side effects occurred before maximum plasma concentrations would have been expected to be reached, then resolved, perhaps suggesting a relationship to the velocity (rather than the degree) of receptor occupancy. This indicates that the AE profile could potentially be even further enhanced with multiple, lower doses and/or with the solid dosage form being used in the ongoing and future studies. There were a few subjects (4/54) experiencing QTc prolongation on '354, though increases were relatively modest (15-35msec). We do not believe these showed any dose dependence, and they were considered by investigators and an outside expert not to pose any risk. We also note that the FDA has not indicated any specific concerns or future monitoring requirements. Nonetheless, this does bear watching in future studies.

**Though '354 has not yet been tested in patients for proof of concept, Concert's receptor occupancy study provides an early read that they might achieve benzodiazepine-like efficacy without sedating side effects.** The company's receptor occupancy study helped answer several critical questions, including whether the '354 dosing level achieved a sufficient receptor occupancy level for desired effects at an adequate therapeutic index compared to marketed benzodiazepines.

- **How does a receptor occupancy study work?** Subjects initially received radiolabeled benzodiazepine (18-F flumazenil) to "saturate" the $GABA_A$ receptors and provide a baseline image. Two weeks later, once the flumazenil "washed out" of their system, subjects were administered '354, followed by the radiolabeled benzodiazepine, and rescanned. The difference in signal intensity with and without '354 can be depicted visually to indicate how much '354 is binding to the receptors (and blocking the radiolabeled benzodiazepine from binding). Concert conducted the study with a total of nine subjects, testing doses of 4, 20, 40, and 60mg.
- **What did the receptor occupancy study show**? The study suggested dose-dependent receptor occupancy through 24 hours post-dosing, plateauing at the 40mg dose. In particular, just one 20 mg dose of '354 provided $GABA_A$ receptor occupancy of 63% and 60% at five hours and 24 hours following dosing.

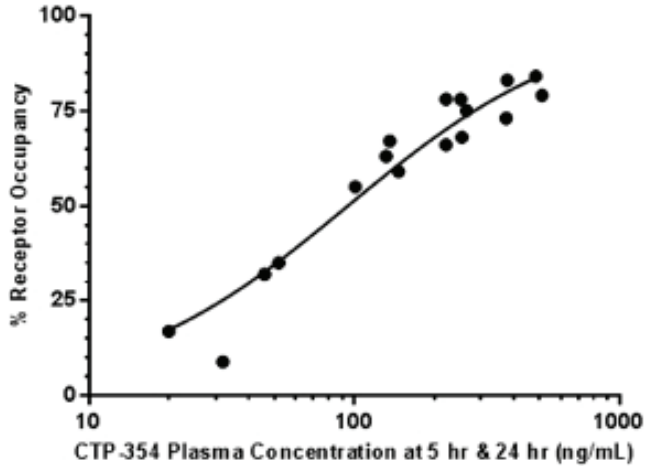
**Exhibit 9. Average $GABA_A$ receptor occupancy for '354 at five hours and 24 hours after dosing**

| CTP-354 Dose (mg) | Number of subjects | Average $GABA_A$ receptor occupancy at 5hrs after dosing | Average $GABA_A$ receptor occupancy at 24hrs after dosing |
|---|---|---|---|
| 4 | 2 | 0.34 | 0.13 |
| 20 | 2 | 0.63 | 0.6 |
| 40 | 3 | 0.79 | 0.71 |
| 60 | 2 | 0.82 | 0.76 |

Source: Company reports and Wells Fargo Securities, LLC (used with company permission).

There also looked to be a clear correlation between $GABA_A$ receptor occupancy and plasma '354 concentrations. In particular, plasma concentrations of '354 greater than 100 ng/mL corresponded with $GABA_A$ receptor occupancies greater than 50%.

**Exhibit 10. '354 $GABA_A$ Receptor Occupancy versus Plasma Concentration in Healthy Volunteers**




Source: Concert Pharmaceuticals S-1, filed January 2014

- **How does this compare to other agents?** First, at doses at least as high as those advised in the label, $GABA_A$ receptor occupancies of several marketed non-selective benzodiazepines were calculated to be 16-24%, with development of sedation seen at those levels, as well. Benzodiazepines thus cause sedation at low receptor occupancy levels. In comparison, the fact that no sedation, ataxia, or similar AEs were seen at the two lower doses of '354 used yet in these doses led to $GABA_A$ receptor occupancies of 34-63% suggest that '354 is effectively hitting substantial numbers of $GABA_A$ receptors at 4mg and 20mg single doses, while avoiding the undesirable α1 related side effects.

- **What are some of the limitations to interpreting these data?** One key limitation is that this study was performed with a small number of volunteers, and there is likely some intra-study variability from subject to subject that may introduce some bias. In addition, while PK models predict 6mg daily is equivalent to a 20mg single dose, this still needs to be confirmed in a multi-dose study. Furthermore, the relationship between plasma '354 concentrations and receptor occupancy requires exploration in the upcoming multiple ascending dose study. Careful analysis of the extent of accumulation of '354 during a repeated dosing period is needed, in our view, as it could theoretically increase side effects such as sedation over time (though the lower, multiple doses reducing the velocity of receptor occupancy could offset this). Finally, since the receptor occupancy study only assesses the drug's interaction with $GABA_A$ and not its individual subtypes, it is necessary to hold proof-of-concept studies in patients to definitively confirm interaction with the appropriate alpha subtypes desired for efficacy.

**Ongoing and Future Trials**

**CNCE commenced a phase Ib multiple ascending dose study in Q1 2014, also with an imaging component, which we believe will be important for defining the target interactions and side-effect profile over multiple doses.** This trial is a ten-day multiple ascending dose study in up to 62 healthy volunteers, with initial data expected to be reported in H2 2014. Assessed in the trial are to be the 2mg and 6mg doses. Although these are slightly lower than the doses they were originally planning to explore, the company's extensive PK modeling and that of PK specialists indicated to them that 6mg of '354 with repeated dosing may provide at least 60% receptor occupancy, comparable to the 20mg single dose, which caused saturation of $GABA_A$ receptor occupancy at 24 hours. The half-life for the 6mg dose is 17-18 hours, suggesting the potential for once-daily dosing at this dose level. The study is to explore also different formulations of the dosing (initially liquid suspension, with possible subsequent crossover into solid dose formulation, which should be important for future studies and commercial viability), as well as the effects of taking '354 with food, compared to fasting. PET imaging is to be examined at the 6mg dose, and we believe this could provide important corroboration of receptor occupancy properties at a steady state.

**Though the FDA has placed '354 on partial clinical hold, preventing higher doses from being studied, we do not believe this arose from any safety concern and believe this can be addressed, if need be, with additional preclinical work.** In November 2013, FDA's Division of Neurology Products placed the program on partial clinical hold, precluding CNCE from exploring doses higher than a 60mg single dose or 6mg multiple doses. Though somewhat unusual, based on our discussion with the company, it appears this is not related to any specific concerns, with the agency noting minimal if any toxicities, and likely represents FDA conservatism as CNCE tested significantly higher single dose exposures in animals (i.e., 15 mg/kg single doses in male beagles, which weigh, on average, 10 kg). Though multiple 6mg doses may be sufficient to achieve 60% receptor occupancy and potential efficacy in the spasticity indication, CNCE plans to run an additional preclinical toxicology study at higher doses that would enable them to escalate further, for spasticity or other indications. The partial clinical hold should not otherwise affect '354's clinical development plans, including the planned phase II study.

**We believe spasticity makes sense as the first indication in which to explore proof of concept for '354.** In H2 2014, following completion of the MAD study, CNCE plans to conduct two phase II studies in spasticity, one in MS-related spasticity and one in spasticity related to spinal cord injury (SCI). Though the trial designs are being finalized, they will likely consist of a 2x2-week placebo-controlled crossover in patients titrated off of their existing medications. Based on historical studies, we believe it will take approximately a 200-patient study 1.5 years to enroll, meaning data could be available end-2015/early-2016, with a phase III potentially starting around mid-2016. The spasticity indication provides a relatively straightforward way to assess the efficacy/safety balance, though we note the Ashworth scale commonly used as a primary endpoint (thought this may be evolving) is a relatively blunt instrument that may be affected by variability, so study conduct should be important.

**Market Opportunity**

**Though not massive, the spasticity market would provide a meaningful initial opportunity for '354, especially if the drug proves clearly differentiated on dosing and side effects from currently-available therapies.** Currently, the most commonly used drugs to treat spasticity are baclofen and tizanidine, with intrathecal baclofen, benzodiazepines, botulinum toxin, and gabapentin also prescribed. Physicians have indicated to us that baclofen is reasonably well tolerated for patients at its starting doses, but in some patients requiring dose escalation, due to insufficient efficacy, side effects like somnolence, weakness, and mental cloudiness begin to mount. Tizanidine also causes sedation. This is important, especially in MS, where maintaining quality of life (mobility, alertness) is key, in our view. The drugs are also required to be dosed up to 4x/day. Given the broad experience with baclofen and tizanidine, as well as the lack of head-to-head studies, we would expect most physicians would reserve a potential new branded therapy like '354 for patients inadequately responding to or tolerating the existing generics; in addition, we would expect insurance companies to require step edits, with generic agents being preferred front-line treatments. Still, the proportion of patients having side effects to currently-available medicines and needing a better agent may be sizeable. We note that sales of Acorda's Zanaflex capsules, an immediate-release formulation of generic tizanidine with a slightly smoother exposure curve, reached $61 million in 2011, before the capsules themselves went generic, though we believe a 1x/day dosed agent with meaningfully less sedation could have sales substantially higher than this.

**We believe sales in spasticity could reach $221 million by 2022E.** Up to 350,000 Americans with MS and 311,000 Americans with SCI are believed to have varying degrees of spasticity (Adams 2005, Rizzo 2004). Our patient-based revenue build for CTP-354 includes indications in both MS and SCI. We stratify U.S. and EU MS patients based on spasticity and apply a spasticity rate of 35% in each market, estimating conservative numbers of about 152,000 and about 149,000 patients in 2014, respectively. We estimate '354 reaches market in the United States by 2020E and ramps up from an initial 10% penetration rate as second-line therapy in MS spasticity to 25% by 2023E, and from an initial 7% penetration as second-line in SCI spasticity to 22% by 2023E. We believe '354 will first be tried in treatment-refractory cases, and our first-line estimates are incrementally lower. End-user sales in this scenario reach $155 million in the United States and $221 million globally by 2022E.

## Exhibit 11. CTP-354 Spasticity Revenue Build

| Spasticity Market | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E |
|---|---|---|---|---|---|---|
| US population | 322,292,786 | 325,193,421 | 328,120,162 | 331,073,244 | 334,052,903 | 337,059,379 |
| Multiple sclerosis | | | | | | |
| MS prevalence (%) | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% |
| MS prevalence pool | 451,210 | 455,271 | 459,368 | 463,503 | 467,674 | 471,883 |
| MS spasticity rate (%) | 35% | 35% | 35% | 35% | 35% | 35% |
| MS spasticity prevalence pool | 157,923 | 159,345 | 160,779 | 162,226 | 163,686 | 165,159 |
| 1st line treatment rate (%) | 50.0% | 50.0% | 50.0% | 50.0% | 50.0% | 50.0% |
| 1st line treatments | 78,962 | 79,672 | 80,389 | 81,113 | 81,843 | 82,580 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *5.0%* | *10.0%* | *15.0%* | *20.0%* |
| CTP-354 treated | 0 | 0 | 4,019 | 8,111 | 12,276 | 16,516 |
| 2nd line treatment rate (%) | 43% | 43% | 43% | 43% | 43% | 43% |
| 2nd line treatments | 33,954 | 34,259 | 34,567 | 34,879 | 35,192 | 35,509 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *10.0%* | *13.0%* | *18.0%* | *25.0%* |
| CTP-354 treated | 0 | 0 | 3,457 | 4,534 | 6,335 | 8,877 |
| Spinal Cord injury | | | | | | |
| SCI prevalence (%) | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% |
| SCI prevalence pool | 322,293 | 325,193 | 328,120 | 331,073 | 334,053 | 337,059 |
| SCI spasticity moderate/severe (%) | 35.0% | 35.0% | 35.0% | 35.0% | 35.0% | 35.0% |
| SCI spasticity prevalence pool | 112,802 | 113,818 | 114,842 | 115,876 | 116,919 | 117,971 |
| 1st line treatment rate (%) | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| 1st line treatments | 112,802 | 113,818 | 114,842 | 115,876 | 116,919 | 117,971 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *2.0%* | *7.0%* | *12.0%* | *17.0%* |
| CTP-354 treated | 0 | 0 | 2,297 | 8,111 | 14,030 | 20,055 |
| 2nd line treatment rate (%) | 75.0% | 75.0% | 75.0% | 75.0% | 75.0% | 75.0% |
| 2nd line treatments | 84,602 | 85,363 | 86,132 | 86,907 | 87,689 | 88,478 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *7.0%* | *10.0%* | *15.0%* | *22.0%* |
| CTP-354 treated | 0 | 0 | 6,029 | 8,691 | 13,153 | 19,465 |
| Other (post-stroke, CP) | | | | | | |
| Prevalence | 2,388,420 | 2,412,305 | 2,436,428 | 2,460,792 | 2,485,400 | 2,510,254 |
| Off-label penetration | *0.0%* | *0.0%* | *0.2%* | *0.4%* | *0.6%* | *0.8%* |
| CTP-354 treated | 0 | 0 | 4,873 | 9,843 | 14,912 | 20,082 |
| Total number of spasticity patients treated with '354 | 0 | 0 | 20,675 | 39,291 | 60,707 | 84,995 |
| Cost per year of treatment | $2,574 | $2,677 | $2,784 | $2,895 | $3,011 | $3,131 |
| Compliance rate (%) | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% |
| Sales of '354 in U.S. in spasticity ('000s) | $0 | $0 | $48,920 | $96,686 | $155,363 | $226,223 |
| | | | | | | |
| EU population (Major countries) | 530,390,949 | 535,164,467 | 539,980,948 | 544,840,776 | 549,744,343 | 554,692,042 |
| Multiple sclerosis | | | | | | |
| MS prevalence (%) | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% |
| MS prevalence pool | 440,224 | 444,187 | 448,184 | 452,218 | 456,288 | 460,394 |
| MS spasticity rate (%) | 35.0% | 35.0% | 35.0% | 35.0% | 35.0% | 35.0% |
| MS spasticity prevalence pool | 154,079 | 155,465 | 156,864 | 158,276 | 159,701 | 161,138 |
| 1st line treatment rate (%) | 50% | 50% | 50% | 50% | 50% | 50% |
| 1st line treatments | 77,039 | 77,733 | 78,432 | 79,138 | 79,850 | 80,569 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *0.0%* | *5.0%* | *10.0%* | *15.0%* |
| CTP-354 treated | 0 | 0 | 0 | 3,957 | 7,985 | 12,085 |
| 2nd line treatment rate (%) | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% |
| 2nd line treatments | 33,127 | 33,425 | 33,726 | 34,029 | 34,336 | 34,645 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *0.0%* | *10.0%* | *13.0%* | *18.0%* |
| CTP-354 treated | 0 | 0 | 0 | 396 | 1,038 | 2,175 |
| Spinal Cord injury | | | | | | |
| SCI prevalence (%) | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% | 0.1% |
| SCI prevalence pool | 530,391 | 535,164 | 539,981 | 544,841 | 549,744 | 554,692 |
| SCI spasticity moderate/severe (%) | 35.0% | 35.0% | 35.0% | 35.0% | 35.0% | 35.0% |
| SCI spasticity prevalence pool | 185,637 | 187,308 | 188,993 | 190,694 | 192,411 | 194,142 |
| 1st line treatment rate (%) | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |
| 1st line treatments | 185,637 | 187,308 | 188,993 | 190,694 | 192,411 | 194,142 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *0.0%* | *2.0%* | *7.0%* | *12.0%* |
| CTP-354 treated | 0 | 0 | 0 | 3,814 | 13,469 | 23,297 |
| 2nd line treatment rate (%) | 75.0% | 75.0% | 75.0% | 75.0% | 75.0% | 75.0% |
| 2nd line treatments | 139,228 | 140,481 | 141,745 | 143,021 | 144,308 | 145,607 |
| CTP-354 penetration (%) | *0.0%* | *0.0%* | *0.0%* | *7.0%* | *10.0%* | *15.0%* |
| CTP-354 treated | 0 | 0 | 0 | 10,011 | 14,431 | 21,841 |
| Total number of spasticity patients treated with '354 | 0 | 0 | 0 | 18,178 | 36,923 | 59,399 |
| Cost per year of treatment | $1,802 | $1,874 | $1,949 | $2,027 | $2,108 | $2,192 |
| Compliance rate (%) | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% |
| Sales of '354 in Europe in spasticity ('000s) | $0 | $0 | $0 | $31,312 | $66,145 | $110,667 |
| Royalties on EU '354 sales ('000s) | $0 | $0 | $0 | $5,323 | $11,245 | $18,813 |
| | | | | | | |
| **Worldwide sales of '354 in spasticity ('000s)** | **$0** | **$0** | **$48,920** | **$127,999** | **$221,508** | **$336,890** |
| **Worldside revenues from '354 in spasticity ('000s)** | **$0** | **$0** | **$48,920** | **$102,009** | **$166,608** | **$245,037** |

Source: Company reports and Wells Fargo Securities, LLC estimates

**'354 also has opportunity outside of MS and SCI as it is potentially applicable to spasticity associated with other neurologic conditions such as stroke, cerebral palsy, and traumatic brain injury.** The spasticity associated with these conditions can be severely debilitating, and the currently available oral treatments may provide only partial relief and carry side effects such as sedation or be limited in other respects. Non-oral medical therapies include botulinum and intrathecal baclofen. For example, CP-associated spasticity is preferentially treated with botulinum toxin, but patients may develop antibodies that reduce the efficacy of the treatment, and the injection carries a risk of systemic side effects. Intrathecal baclofen therapy also reduces spasticity associated with spinal cord injury and CP, though it is associated with a range of complications including CSF leakage, bleeding, and infection. We believe that such patients with stroke, CP, and TBI spasticity who either have not responded adequately to other anti-spasticity medications, or are limited by their complications, may see potentially clinically significant improvement on '354, which represents significant additional market opportunities for Concert. U.S. CP prevalence is believed to be 765,000 patients (CDC). There are thought to be 7.0 million stroke survivors, with up to 60% affected by spasticity (National Stroke Association), and sources indicate that there are 3.2 million people living with some disability following TBI (Journal of Head Trauma Rehabilitation). Given the limitations of current treatment options for these patients, we believe there is significant opportunity for off-label use of '354, which could potentially lead to upside to our estimates.

**Use of '354 in indications beyond spasticity, such as anxiety and pain, where benzodiazepines are used currently, could potentially provide significant upside opportunity long term.** Depending on proof-of-concept efficacy results and safety data, we believe Concert will explore expanded uses for '354 in broader indications such as anxiety and pain. Our sense from speaking with the company is that it will likely focus on certain defined sub-populations, such as patients unable to tolerate existing therapies, or who might be predicted to have a lesser response or greater side effects to available treatments, to help optimize the potential clinical, regulatory, and reimbursement pathways. Though the next steps have yet to be established, given the size of these indications (severe generalized anxiety disorder alone is a potential market opportunity of about 6.4 million patients in the United States and Europe) and considerable need for a better tolerated benzo-like drug for these indications, we believe this could be a meaningful expanded opportunity in the long term for '354, as high as another $240 million by 2023 and significantly more beyond this.

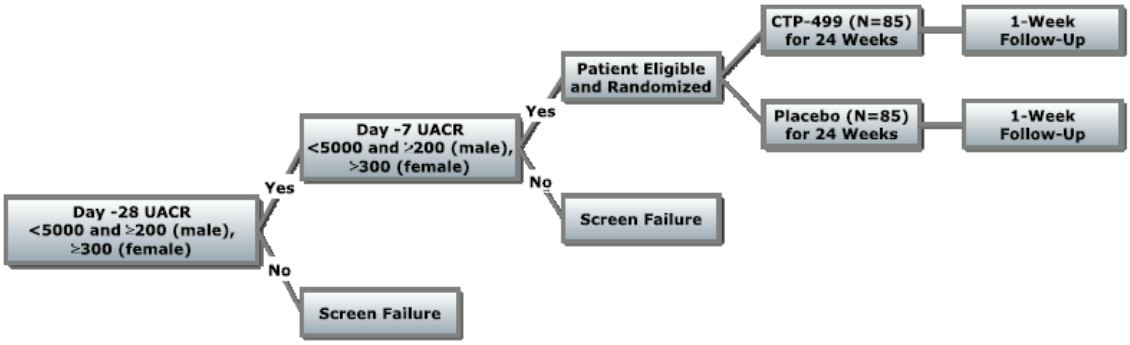
## CTP-499

**Overview. CTP-499 is a multi-subtype selective PDE inhibitor currently completing a phase II proof-of-concept study in diabetic kidney disease.** The drug, a deuterated metabolite (HDX) of pentoxifylline, a drug approved for leg claudication, is completing a multi-part phase II trial in diabetic nephropathy. Thus far, 24-week primary endpoint data and preliminary 48-week results have been presented; '499 did not meet statistical significance in its primary endpoint, but showed some potential signals of renal protective activity, particularly with the longer follow-up after 48 weeks. Following final analysis of the 48-week results, CNCE plans to meet with the FDA mid-2014 to discuss a potential regulatory path forward, and then out-license the agent for further development. Though it was initially discovered as part of an R&D agreement with GSK, the agreement expired in 2012 and CNCE currently owns all rights to the agent without obligation (other than up to a non-material $2.75 million payment to GSK upon CTP-499 commercialization).

**Phase II Proof-Of-Concept Study**

**In phase II, '499 showed some possible signals of activity in protecting kidney function, though the data are not entirely clear-cut.** In the double-blind phase II study, 182 patients with mild to moderate diabetic kidney disease (eGFR 23-89 mL/min/1.73m²) with macro-albuminuria (UACR ≥200mg/g in males or ≥300mg/g in females) were randomized to receive '499 600mg twice a day versus placebo. The primary endpoint was the change in UACR assessed at 24 weeks, and an additional blinded period was carried out to week 48 and included 143 of the patients (124 of whom completed the full 48 weeks), assessing multiple other measures of kidney function.

**Exhibit 12. CTP-499 phase II study design in diabetic kidney disease**




Source: Sabounjian, et al, 2012, National Kidney Foundation 2012 Spring Clinical Meeting

The final top-line results for UACR changes in patients receiving '499 versus placebo through week 48 are expected to be reported in H1 2014, and an additional open label extension should yield further long-term follow-up data in the future.

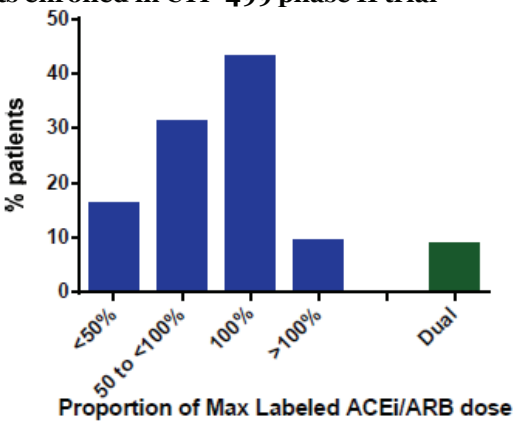
**We explore some of the evidence for potential activity, as well as risks to interpreting the data in the text that follows.** Exhibit 13 summarizes the baseline characteristics of the patients enrolled in the study, and we examine the different sets of results reported to data and how they influence the drug's probability of success:

**Exhibit 13. Baseline characteristics of diabetic CKD patients enrolled in CTP-499 phase II trial**

| Age | | Race, n (%) | |
|---|---|---|---|
| Mean | 63.7 yrs | White | 121 (68.4) |
| Media | 65.0 yrs | Black | 42 (23.7) |
| Range | 29.0 – 86.0 yrs | Asian | 9 (5.1) |
| Number (%) < 65 yrs | 92 (52.0) | Native Hawaiian or Pacific Islander | 2 (1.1) |
| Number (%) >65 yrs | 85 (48.0) | Multiple Races | 3 (1.7) |

| Baseline Parameters | | |
|---|---|---|
| | Mean (± SD) | Median |
| eGFR (mL/min/1.73m²) | 46.0 ± 15.4 | 44.7 |
| UACR (mg/g) | 1086.8 ± 791.2 | 852.1 |
| Serum Creatinine (mg/dL) | 1.67 ± 0.51 | 1.60 |
| BP Systolic (mm Hg) | 131.8 ± 10.4 | 134.0 |
| BP Diastolic (mm Hg) | 75.0 ± 9.2 | 76.0 |
| HbA1c (%) | 7.5 ± 1.4 | 7.4 |
| Serum albumin (g/dL) | 4.1 ± 0.38 | 4.1 |
| Potassium (mEq/L) | 4.4 ± 0.40 | 4.4 |
| Phosphorus (mg/dL) | 3.7 ± 0.53 | 3.7 |
| Duration of diabetes (years) | 16.3 ± 8.9 | 15.4 |
| Duration of CKD diagnosis (years) | 4.3± 4.4 | 3.1 |

*5 patients excluded due to major protocol violation

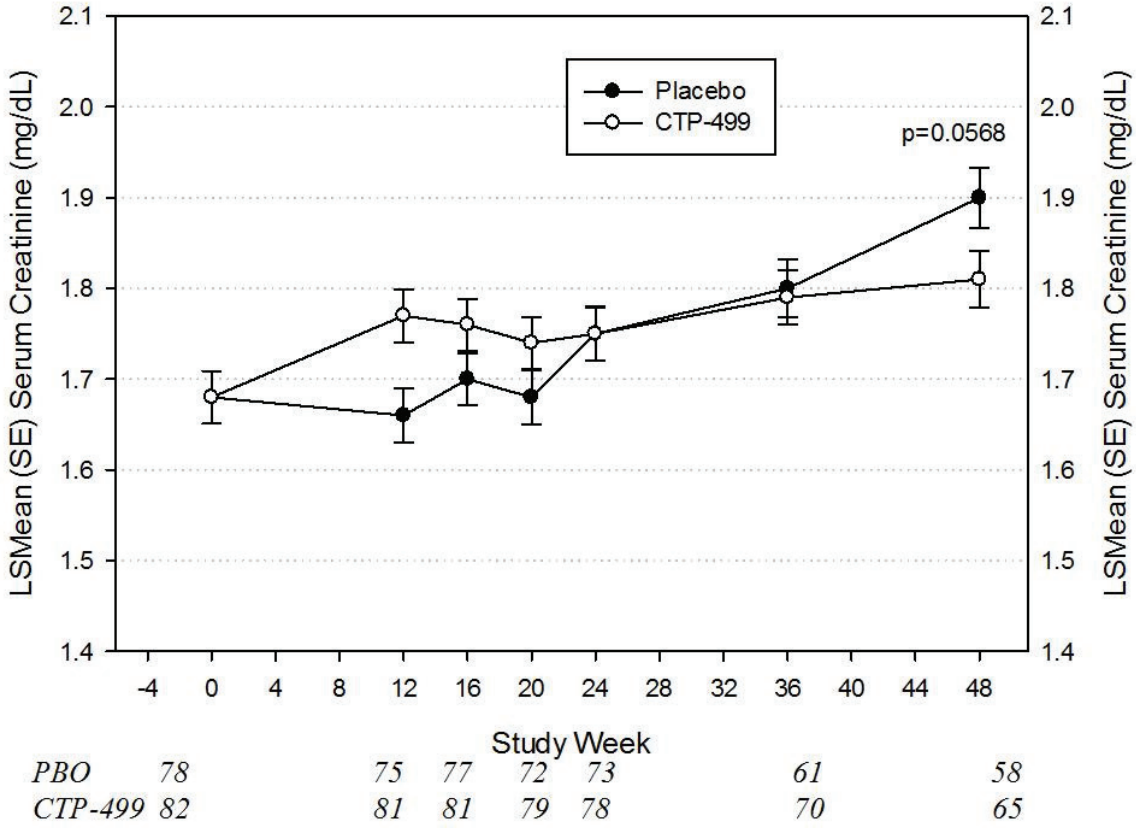



| Stratification Groups | n (%) |
|---|---|
| UACR <1500 and eGFR <45 | 67 (37.9) |
| UACR <1500 and eGFR ≥45 | 67 (37.9) |
| UACR ≥1500 and eGFR <45 | 23 (13.0) |
| UACR ≥1500 and eGFR ≥45 | 20 (11.3) |

Source for chart and tables: Sabounjian, et al, 2013, American Society of Nephrology Kidney Week 2013

- **The trial failed to meet its primary endpoint of UACR at 24 weeks, though it showed some positive trends on longer term follow-up.** UACR, or the urinary albumin/creatinine ratio, is a measure of albumin (protein) "spilled" into the urine by a damaged kidney. Though not a regulatory endpoint, it is typically viewed by key opinion leaders, several of whom we spoke with, as a surrogate for what would translate to protection of renal function over time. In the trial, there were no differences between '499 and placebo at the 24-week time point, though there were trends favoring '499 at week 48, a 2% increase in UACR, versus a 21% increase in the placebo arm. This was somewhat surprising to us, given more rapid additive antiproteinuric effects observed with pentoxifylline in small historical pilot studies, and could be explainable by the challenges showing additive reductions on top of ACE-inhibitors and ARBs. Still, while a more rapid and pronounced effect on UACR would have made the overall dataset clearer, given that UACR improvement is not a registrational endpoint and there is recent evidence that for add-on agents it may not necessarily predict renal protection anyway, we believe there is a reasonable possibility that '499 is conferring benefit despite this primary endpoint miss.
- **Some positive trends toward overall improvements in renal function were observed.** On measures of serum creatinine, a marker of kidney function, the mean increases (indicating worsening functioning) were less for '499, 0.13mg/dL, than for placebo, 0.21mg/dL, suggesting a 38% improvement at week 48. This was nearly statistically significant (p=0.06) and would have been so using a less conservative one-sided t-test (which could have been applied, as one-tailed hypothesis tests are commonly used in phase II trials and a rationale for their use here could be based on an expectation of clinical benefit versus a two-sided test that enables discrimination of an effect in either direction). The measure utilized a least mean squares analysis, to take into account the entirety of the overall data set from weeks 0-48; looking solely at means from baseline to week 48 the differences (and potential benefits from '499) look less marked (1.65 → 1.82 for '499, +0.17, vs. 1.70 → 1.90 for placebo, +0.20). Additionally, the serum creatinine levels showed the effect of worsening (increasing) at the start of '499 treatment before leveling out and eventually demonstrating more stability versus placebo through week 48 (see Exhibit 14).

**Exhibit 14. Preliminary results demonstrate a trend for lower creatinine in '499 arm, with a nearly statistically significant increase in creatinine after 48 weeks (p = 0.06)**




Source: Company reports and Wells Fargo Securities, LLC (used with company permissions)

The shape of the curves may call into question whether CTP-499 has a true, consistent treatment effect or whether the numbers are simply a result of noise. However, there are several things that we believe point to a greater likelihood of a real treatment effect:

- *Similar effects observed with ACEs and ARBs.* Other therapies like ACE inhibitors and ARBs have been shown to produce an initial creatinine elevation and GFR decline, thought to be related to decreases in glomerular pressure that ultimately stabilizes and, counterintuitively, may actually correlate with better long-term renal protection. The mechanism for this increase is thought to arise from an initial fall in GFR, causing a reduction in intraglomerular capillary pressure. These drugs decrease GFR by modulating angiotensin II levels, which vasoconstrict the efferent arterioles of the kidney glomeruli to increase GFR. Clinically, the rise in serum creatinine typically occurs early, and usually peaks in a week from starting the ACE inhibitor. In practice, a 30% increase in serum creatinine above baseline that stabilizes within the first several months of therapy is not considered an indication for discontinuing the ACE inhibitor. We do note, however, that the mechanism by which '499 might have such similar effects is unknown.
- *Near statistical significance.* The fact that these results were near statistical significance speaks to a greater likelihood of true activity versus noise/variability.
- *Less likely bias from dropouts.* One concern might be that there were fewer patients in the study during the second 24 weeks, so theoretically, patients who were worse off (having lesser benefits and/or more side effects) may have stopped participating after the first 24 weeks, biasing the 48-week results in favor of the '499 arm. Though this remains a possibility, the company has done extensive analysis of reasons for discontinuation, eGFR/Cr changes for dropouts relative to the broader group, and indications of poor tolerability and from the collected data was not able to determine any clear differences that would have biased the 48-week results.

Additional follow-up data from the extension study, as well as biomarker data, should help clarify this potential signal and shed more light on potential mechanistic explanation for these curves.

- **Though overall trends on eGFR were not meaningful, '499 appeared to protect against major kidney function declines, something that could potentially bode well for phase III success.** eGFR, or estimated glomerular filtration rate, is a measure that utilizes biomarkers and patient characteristics to triangulate the kidney's functional ability. Though there were not meaningful differences at 48 weeks in mean eGFR levels, when a "threshold" analysis was performed, fewer patients on '499 had 30+% eGFR declines (6% versus 14%) and 40% eGFR declines (2% versus 5%). These were not statistically significant, likely due to the small numbers. However, they were prespecified (not post-hoc) analyses and similar effects were observed in reducing large increases in creatinine, helping corroborate these effects. Though the exact U.S. regulatory path for new CKD drugs is still not completely established, we believe reductions in the proportion of patients with dramatic reductions in kidney function would resonate well as they might lessen the numbers of patients with hastened progression to dialysis. Indeed, a National Kidney Foundation workshop held in December 2012 recommended 30% or 40% GFR declines to the FDA as optimal surrogate endpoints for registration, down from the prior halving of GFR (measured as a doubling of serum creatinine).
- **Greater effects seen in patients with greater baseline proteinuria could allow for a smaller, more focused phase III program.** Nearly all the patients with 30+% eGFR declines had higher (above median) UACR/proteinuria at baseline, indicating such patients are more prone to greater declines that they could potentially be protected from with a drug like '499. One positive is that this could enable a future phase III program to be enriched, by enrolling only higher baseline UACR patients, though a downside risk to this is that it could limit the ultimate applicable/labeled indication. Being a post-hoc analysis, there are some limitations to interpreting this. However, we do note that a recently published study of pentoxifylline, though a retrospective one and not in exactly the same patient population, suggests that this could be a true mechanistic effect, as it showed patients with higher urine protein to creatinine ratios (≥1g/g versus <1g/g) had greater benefits on renal outcomes if they took pentoxifylline, compared to those who did not.

**CTP-499 was reasonably well tolerated, though GI side effects were observed.** The fact that the drug is a deuterated version of one of the major metabolites of an agent available since the early 1970s, in our view, helps reduce theoretical safety risks, though of course any differences in metabolism and/or bio-distribution fostered by the deuteration could create a different side-effect profile. In terms of serious observations, there were two deaths for '499 in the 24-week portion, versus none for placebo, though neither was deemed to be drug related and rates of CV disorders were lower for '499. The SAEs were generally balanced, with serious and non-serious infections more frequent in the '499 arm, for reasons that are unclear (there is not believed to be any immunomodulatory or anti-inflammatory effect that would cause this). GI side effects, the most problematic tolerability issue with pentoxifylline, according to our KOL feedback, and an issue that Concert aimed to dial out through the more renally distributed active metabolite, were still present, though appeared to be more frequent in the treatment arm. A summary of the adverse events occurring in greater than 10% of trial patients is presented in Exhibit 15. We note that no serious adverse events were attributed by trial investigators to drug treatment, and none occurred in greater than 5.7% of patients in either arm of the trial.

**Exhibit 15. Summary of adverse events seen in part 1 of the phase II trial**

| Adverse events with at least 10% incidence | Placebo (n=88) | CTP-499 (n=89) |
|---|---|---|
| Gastrointestinal disorders | 20 (22.7%) | 9 (10.1%) |
| Infections | 14 (15.9%) | 24 (27.0%) |
| Vascular disorders | 14 (15.9%) | 8 (9.0%) |
| Peripheral edema, fatigue, and fever | 11 (12.5%) | 10 (11.2%) |
| Nervous system disorders | 8 (9.1%) | 10 (11.2%) |
| Musculoskeletal and connective tissue disorders | 6 (6.8%) | 10 (11.2%) |
| Respiratory and thoracic disorders | 6 (6.8%) | 9 (10.1%) |
| Endocrine disorders | 4 (4.5%) | 9 (10.1%) |
| Metabolism and nutritional disorders | 9 (10.2%) | 3 (3.4%) |

Source: Concert Pharmaceuticals S-1, filed January 2014

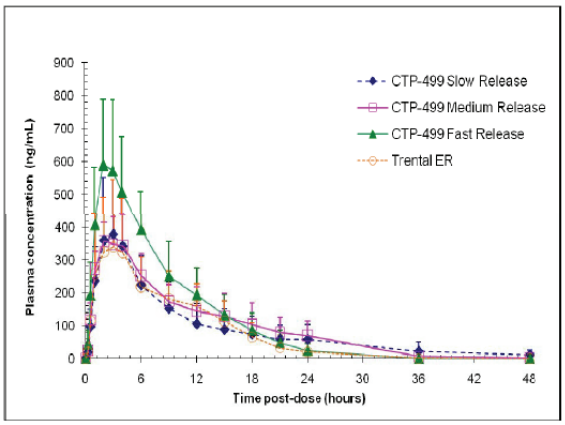
### Earlier Studies and Preclinical Work

**Earlier studies and preclinical work guided dose selection, indicated good safety, and suggested the potential for treatment benefits.** Concert conducted multiple studies prior to phase II, including preclinical work, two phase I studies, a food-effect study, and a phase Ib study to assess the safety, tolerability, and PK of CTP-499in CKD patients. Preclinical data showed that '499 reduced UACR and renal hypertrophy in a streptozocin-induced diabetic rat model, and reduced tubular apoptosis and renal fibrosis in a ureteral obstruction-rate model, with lower plasma concentrations than in humans. Phase I data in healthy volunteers are summarized in Exhibits 16 and 17.

**Exhibit 16. Phase I study of '499 as 200mg slow, medium, or fast release; exposure to active metabolite doubled for '499 compared to Trental; medium release selected for development**

***Pharmacokinetics***

Mean (SD) Plasma CTP-499 or HDX Concentration versus Time




Ratio of $AUC_{last}$ for CTP-499 or Metabolite to the Corresponding Species from Trental

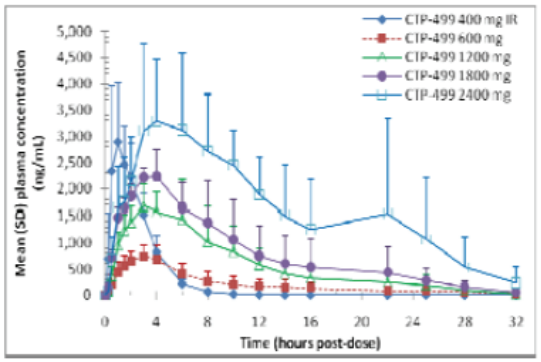
| | CTP-499 | C-21256 | M2 | M3 | M4 | M5 |
|---|---|---|---|---|---|---|
| Fast Release | 1.5 | 1.6 | 2.6 | 0.3 | 1.1 | 0.9 |
| Medium release | 1.2 | 1.1 | 2.2 | 0.2 | 0.9 | 0.8 |
| Slow Release | 1.1 | 1.0 | 2.0 | 0.3 | 0.7 | 0.6 |

Source for graph and table: Parasrampuria et al, 2011, American Society of Nephrology Kidney Week 2011

**Exhibit 17. Phase I study of '499 showing 200mg continuous release (CR) tablets well tolerated at single doses up to and including 1,800 mg, indicating potential for once□daily dosing**

***Pharmacokinetics***

Mean (SD) Plasma CTP-499 Concentration vs Time (Parts A and B)




Comparison of dose-normalized plasma CTP-499 PK parameters by treatment

| PK parameter (unit) | Statistic | Treatment Comparison | | | |
|---|---|---|---|---|---|
| | | 600 mg: 400 mg IR | 1200 mg: 400 mg IR | 1800 mg: 400 mg IR | 2400 mg: 400 mg IR |
| Cmax (ng/mL) | Ratio | 0.18 | 0.21 | 0.19 | 0.22 |
| | 90% CI | 0.14 – 0.25 | 0.15 – 0.28 | 0.14 – 0.26 | 0.16 -0.30 |
| | p-value | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| AUClast (ng*h/mL) | Ratio | 0.48 | 0.68 | 0.62 | 0.98 |
| | 90% CI | 0.32 – 0.72 | 0.45 – 1.03 | 0.41 – 0.94 | 0.65 – 1.48 |
| | p-value | 0.0052 | 0.1244 | 0.0618 | 0.9308 |

Source for graph and table: Parasrampuria et al, 2011, American Society of Nephrology Kidney Week 2011

In the phase Ib CKD study, the company has said some trends on biomarkers were observed, but that the placebo group was too small to draw any definitive conclusions.

**Market Opportunity**

**We believe the market opportunity would be very significant for a drug with a novel mechanism that can complement existing standard of care given the large addressable population.** According to the American Diabetes Association, in 2013, nearly 26 million people in the United States had diabetes, with 90-95% afflicted by type 2 diabetes. An additional 79 million adult Americans have pre-diabetes. As diabetes is the leading cause of CKD and accounts for about 40% of ESRD patients in the United States, the potential market opportunity is significant, and stands to grow given the increasing prevalence of type II diabetes in the United States. While diabetes is less a driver of CKD prevalence in Europe, globally, according to an epidemiology forecast from GlobalData, in 2012, seven of the world's major pharmaceutical markets (the United States, France, Germany, Italy, Spain, the United Kingdom, and Japan) had more than 14 million total prevalent cases of diabetic nephropathy among diagnosed diabetics, with growth expected at an annual rate of 4.2% to almost 20 million total cases by 2022E. These patients with ESRD resulting from diabetic CKD impose significant cost pressures on the health systems of these countries. In the United States, spending on ESRD from CKD constituted approximately 1.3% of Medicare beneficiaries, while accounting for 8.0% of Medicare spending ($33 billion), according to the 2012 United States Renal Data Survey. Current therapies based on angiotensin modulation via ACE inhibitors and ARBs have been proven to be protective of kidney function in diabetic CKD, slowing the decline of kidney function and reducing albuminuria. The use of these therapies has helped slow the growth of ESRD in the population at large. While the main measure of the effect of '499 is not in treating the underlying diabetes, we believe '499's may offer some advantages over existing agents, and should compete strongly in the marketplace as a complement to angiotensin modulation, to further slow progression toward kidney failure. We believe the regulatory pathway to market for '499 may allow it to reach the U.S. market by 2020. We anticipate initiation of a phase III by 2015, after Concert's successful partnering with a development/commercial partner and completion of a phase III by 2018, with filing of an NDA soon afterwards. Assuming Concert captures 12% of the U.S. population, pricing growing to about $8,000 per year (accounting for the subpopulation with greatest macroalbuminuria), we estimate total worldwide sales of approximately $920 million by 2023E, generating royalties of $138 million to Concert in 2023E.

**Exhibit 18. CTP-499 Revenue Build**

| Diabetic CKD Market | 2018E | 2019E | 2020E* | 2021E | 2022E | 2023E |
|---|---|---|---|---|---|---|
| US population | 322,292,786 | 325,193,421 | 328,120,162 | 331,073,244 | 334,052,903 | 337,059,379 |
| US adult population (21 and older) | 239,931,568 | 242,090,952 | 244,269,771 | 246,468,199 | 248,686,413 | 250,924,590 |
| Diabetic Chronic Kidney Disease | | | | | | |
| CKD prevalence (%) | 12.5% | 12.6% | 12.8% | 12.9% | 13.0% | 13.2% |
| CKD prevalence pool | 30,019,955 | 30,593,036 | 31,177,057 | 31,772,227 | 32,378,759 | 32,996,869 |
| Diabetic CKD rate (%) | 38% | 38% | 39% | 39% | 39% | 39% |
| Diabetic CKD prevalence pool | 11,444,798 | 11,721,596 | 12,005,088 | 12,295,436 | 12,592,807 | 12,897,369 |
| Stage I-II | 37.7% | 37.7% | 37.7% | 37.7% | 37.7% | 37.7% |
| Stage III | 57.8% | 57.8% | 57.8% | 57.8% | 57.8% | 57.8% |
| Stage IV | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% |
| Estimated diabetic CKD Stage III pool | 6,619,193 | 6,779,281 | 6,943,241 | 7,111,166 | 7,283,153 | 7,459,299 |
| Patients with eGFR>25 and macroalbuminuria | 1,256,366 | 1,286,751 | 1,317,872 | 1,349,745 | 1,382,389 | 1,415,823 |
| Patients with most severe macroalbuminuria | 628,183 | 643,376 | 658,936 | 674,873 | 691,195 | 707,912 |
| CTP-499 penetration (%) | *1.5%* | *3.0%* | *4.5%* | *6.0%* | *7.5%* | *9.0%* |
| Total number of CKD patients treated with '499 | 18,845 | 38,603 | 59,304 | 80,985 | 103,679 | 127,424 |
| Cost per year of treatment | $6,327 | $6,580 | $6,843 | $7,117 | $7,401 | $7,697 |
| Compliance rate (%) | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% |
| Sales of '499 in U.S. in CKD ('000s) | $101,344 | $215,893 | $344,938 | $489,883 | $652,250 | $833,695 |
| Royalties on '499 U.S. sales: 15% ('000s) | $15,202 | $32,384 | $51,741 | $73,482 | $97,837 | $125,054 |
| | | | | | | |
| EU population (Major countries) | 530,390,949 | 535,164,467 | 539,980,948 | 544,840,776 | 549,744,343 | 554,692,042 |
| EU adult population (21 and older) | 412,653,623 | 416,367,506 | 420,114,813 | 423,895,847 | 427,710,909 | 431,560,308 |
| Diabetic Chronic Kidney Disease | | | | | | |
| CKD prevalence (%) | 11.7% | 11.8% | 11.9% | 12.0% | 12.2% | 12.3% |
| CKD prevalence pool | 48,184,415 | 49,104,255 | 50,041,656 | 50,996,951 | 51,970,483 | 52,962,599 |
| Diabetic CKD rate (%) | 16% | 16% | 16% | 16% | 17% | 17% |
| Diabetic CKD prevalence pool | 7,672,309 | 7,896,961 | 8,128,191 | 8,366,192 | 8,611,162 | 8,863,304 |
| Stage I | 45.5% | 45.5% | 45.5% | 45.5% | 45.5% | 45.5% |
| Stage II-III | 41.8% | 41.8% | 41.8% | 41.8% | 41.8% | 41.8% |
| Stage IV | 6.4% | 6.4% | 6.4% | 6.4% | 6.4% | 6.4% |
| Estimated Diabetic CKD Stage III pool | 10,074,923 | 10,267,253 | 10,463,255 | 10,662,999 | 10,866,555 | 11,073,998 |
| Patients with eGFR>25 and macroalbuminuria | 688,415 | 708,573 | 729,320 | 750,676 | 772,656 | 795,280 |
| Patients with most severe macroalbuminuria | 344,208 | 354,286 | 364,660 | 375,338 | 386,328 | 397,640 |
| CTP-499 penetration (%) | *0.0%* | *0.5%* | *2.0%* | *3.5%* | *5.0%* | *6.5%* |
| Total number of CKD patients treated with '499 | 0 | 1,771 | 7,293 | 13,137 | 19,316 | 25,847 |
| Cost per year of treatment | $3,163 | $3,290 | $3,421 | $3,558 | $3,701 | $3,849 |
| Compliance rate (%) | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% | 85.0% |
| Sales of '499 in EU in CKD ('000s) | $0 | $4,954 | $21,210 | $39,733 | $60,760 | $84,553 |
| Royalties on '499 EU sales: 15% ('000s) | $0 | $743 | $3,182 | $5,960 | $9,114 | $12,683 |
| | | | | | | |
| **Worldwide sales of '499 in CKD ('000s)** | **$101,344** | **$220,846** | **$366,148** | **$529,615** | **$713,010** | **$918,248** |
| **Worldwide revs from '499 in CKD ('000s)** | **$15,202** | **$33,127** | **$54,922** | **$79,442** | **$106,951** | **$137,737** |

Source: Company reports and Wells Fargo Securities, LLC estimates

**Competitive Landscape**

**There are several other competitors worth watching that are also developing molecules for diabetic nephropathy, though the failure of bardoxolone methyl in phase III is a reminder of the risk in this indication.** Notable agents with similar targets are listed below, from preclinical to phase II development.

**Exhibit 19. Notable Other Agents Targeting Diabetic Nephropathy In Development**

| Drug | Company | Approach | Results/Status |
|---|---|---|---|
| Atrasentan | ABBV | Endothelin Receptor Type A (EDNRA) | III |
| Bindarit | ACRAF SpA | Chemokine (C-C motif) Ligand 2 (CCL2)/MCP-1; Chemokine (C-C motif) Ligand 8 (CCL8)/MCP-2; Chemokine (C-C motif) Ligand 7 (CCL7)/MCP-3 | IIb |
| Pyridorin | NephroGenex | Receptor for Advanced Glycation End Products (RAGE) | IIb |
| Baricitinib | LLY/INCY | JAK/STAT | II |
| CCX140 | CCXI | Chemokine Receptor 2 (CCR2) | II |
| Finerenone | Bayer | Mineralcorticoid Receptor | II |
| GKT137831 | GenKyoTex S.A. | NADH Oxidase | II |
| INV-144 | InVasc Therapeutics | Angiotensin II Receptor Type 1 (AT1) | II |
| LY2382770 | LLY | Transforming Growth Factor-beta (TGF-beta) | II |
| NOX-E36 | NOXXON Pharma AG | Chemokine (C-C motif) Ligand 2 (CCL2)/MCP-1 | II |
| PF-0048979 | PFE | Phosphodiesterase 5 (PDE5) | II |
| PF-0463481 | PFE | Chemokine Receptor 5 (CCR5); Chemokine Receptor 2 (CCR2) | II |
| GLY-230 | Glycadia | Cyclooxygenases (COX-1, COX-2, and COX-3) | I/II |
| ABT-614 | ABBV | Dopamine 3 (D3) Receptor | I |
| CCX872 | CCXI | Chemokine Receptor 2 (CCR2) | I |
| GS-4997 | GILD | Apoptosis (Cell Death) | I |
| VTP-27999 | Vitae Pharmaceuticals | Renin | I |
| MT-3995 | Mitsubishi Tanabe Pharma | Mineralcorticoid Receptor | Development Outside U.S. |
| GR-MD-02 | GALT | Galectin-3 | Preclinical |
| SER150 | Serodus AS | Leukotriene receptor/Thromboxane receptor; Thromboxane Synthase | Preclinical |
| VPI-2690B | Vascular Pharmaceuticals | IGF-1R (Insulin-like Growth Factor-1 Receptor) | Preclinical |
| MT-3995 | Mitsubishi Tanabe Pharma | Mineralcorticoid Receptor | Development Outside U.S. |

Source: BioMedTracker, Company reports, and Wells Fargo Securities, LLC

Perhaps the most similar molecule is by Pfizer, which is developing an inhibitor of PDE5, PFE-00489791 for diabetic nephropathy intended to enhance the relaxation of renal blood vessels and reduce blood pressure. That phase II study began in October 2010 and was estimated for completion in August 2013. However, the results had not yet been reported as of the time of Pfizer's last pipeline update on February 28, 2014. We do not believe this necessarily bodes poorly for '499. Recall that '499 is the deuterated form of pentoxifylline, which is a nonselective phosphodiesterase inhibitor; the action of a PDE inhibitor with an enhanced metabolic profile across multiple PDE subtypes might be expected to have broader activity.

## Key Collaborations

**Concert has several partnerships leveraging their deuteration technology for which future milestones and royalties could be obtained.** Concert is eligible to receive up to an additional $12 million in milestones in the near term, including $2 million in 2014 from Avanir for dosing initiation of the AVP-786 phase II trial, $2 million in 2015 from Avanir for other AVP-786 developmental milestones, and $8 million in 2015 from Celgene for completion of a CTP-730 phase I trial. Collectively we believe these partnerships provide additional external valuation of Concert's technology and have the potential to generate meaningful long-term revenue for the company.

- **Celgene.** Formed in April 2013, the partnership with Celgene covers four deuterated compounds with targets in inflammation and cancer. Under the terms of the agreement, Concert received $35 million up front, could receive up to $1.4 billion in milestones collectively, and would receive royalties on future product sales. The first program in the collaboration, CTP-730, is expected to enter the clinic in H2 2014, and we believe could potentially be through phase I studies by end-2015. Though the compound has not been identified, given that its target is inflammatory diseases, we believe it is likely a deuterated version of apremilast (or one of its analogues), or of one of Celgene's inflammation-focused IMiDs, like CC-220. For this initial program, Concert is to conduct and pay for all phase I expenses, following which Celgene would take over development, and Concert can receive up to $8 million for phase I completion (within a total of $23 million in development milestones), $247.5 million in regulatory milestones, and $50 million in sales-based milestones. Though it is difficult to ascribe a precise value to the program without knowing the exact target, we believe a partnership with a company of Celgene's expertise and reputation, as well as a stated interest in purchasing up to $14 million shares in its equity offering, provides strong external validation for Concert's deuteration technology. The market opportunity could also be considerable; if the lead program were a deuterated version of apremilast aimed perhaps at improving dosing to 1x/day from 2x/day and/or other features (which we know is something Celgene is exploring with other strategies), it could potentially capture much of the long-term market opportunity for apremilast, which we estimate to be slightly more than $1 billion by 2018E in psoriatic arthritis, psoriasis, and ankylosing spondylitis.

**Exhibit 20. Summary of CELG partnership terms**

| | |
|---|---|
| **Upfront** | $35M |
| **Potential milestones** | $1.4B |
| **Royalties** | mid-single/low- double digits below 20% |

Source: Company reports and Wells Fargo Securities, LLC

- **Jazz.** The partnership with Jazz was formed in February 2013 and covers deuterated versions of sodium oxybate (D-SXB), the active ingredient in Jazz's marketed narcolepsy product Xyrem. Under the terms of the agreement, Concert received $8 million up front, can receive up to $35 million in regulatory and $70 million in sales milestones, and would receive royalties on future product sales. Concert is responsible for phase I conduct and material, with Jazz reimbursing development costs. Following submission of an investigational medicine product dossier in Europe end-2013, Jazz has received regulatory approval in Europe to initiate a clinical study, and the study is expected to begin this year once sufficient product has been manufactured. Xyrem is on a more than $600 million sales run rate at present (even with relatively low penetration into the diagnosed population), with consensus sales estimates exceeding $1.3 billion by 2018, despite a major shortcoming, a short half-life that requires patients to set an alarm to wake up in the middle of the night for a second dose. If deuteration is able to prolong the drug's half-life to allow patients to take a single dose at night, we believe this would be a considerable advantage. We also believe that given the patent expiries for Xyrem, which range between 2019 and 2024, Jazz will be highly incentivized to move '386 forward as a lifecycle extension strategy if initial PK data are promising (Concert's patent would extent until at least 2030-32). Such approaches, replacing a genericized drug with a less frequently dosed branded version, have had mixed success historically: Follow-on Nuvigil (2012 sales of $347 million) has not come close to reaching peak Provigil sales ($1.2 billion), whereas Effexor XR saw approval in 1997, four years after Effexor, and achieved blockbuster peak sales of $4 billion, easily supplanting sales of the immediate release formulation. Regardless, in this case, we believe the impact of a longer acting version would be very significant to patients, which could drive rapid uptake. Though we ascribe a low probability of success just given the lack of available data and early stage, we believe that if the drug is ultimately approved, it could generate $63 million in revenue for Concert by 2023E and significantly more beyond that.

**Exhibit 21. Summary of JAZZ partnership terms**

| | |
|---|---|
| **Upfront** | $4M |
| **Potential milestones** | $113M |
| **Royalties** | mid-single/low- double digits below 20% |

Source: Company reports and Wells Fargo Securities, LLC

- **Avanir.** The development and licensing partnership with Avanir was formed in February 2012 and covers deuterated dextromethorphan products. Under the terms of the agreement, Concert received $2 million up front and can receive up to $4 million in development, $37 million in regulatory and commercial launch, and $125 million in sales milestones, in addition to receiving royalties on future sales ranging from mid-single digits to low double digits (less than 20%). Avanir has a currently marketed therapy for pseudobulbar affect, Neudexta, as well as a developmental program called AVP-923, both of which consist of dextromethorphan combined with quinidine (as a PK enhancer). The deuteration of dextromethorphan into AVP-786 holds the possibility of maintaining this effect, while enhancing its plasma exposure, and thus, duration of effect, by enhancing resistance to CYP2D6 metabolism. Indeed, phase I data reported in 2013 demonstrated that AVP-786 had comparable exposures to AVP-923 with a substantially lower quinidine dose, which would be desirable given quinidine's known side effects. Avanir plans to file an IND and begin a phase IIa study in treatment-resistant major depressive disorder (MDD) in H2 2014. Although MDD development can be challenging and we do not believe similar drugs have been tested in this indication, there is some mechanistic rationale for exploring it: (1) There are certain pharmacodynamic commonalities between dextromethorphan and anti-depressants or molecules with anti-depressant properties, and dextromethorphan has actions on NMDA and serotonin receptors, similar to ketamine, a rapid-acting antidepressant. (2) In a pseudobulbar effect study, AVP-923 appeared to improve depressive symptoms in certain patients. Though we ascribe a low probability of success given the lack of available data and challenges inherent to MDD development, we believe that if the drug is ultimately approved in 2019, it could generate $41 million in revenue for Concert by 2023. In addition, other potential indications could be explored and potentially provide upside opportunities. Finally, perhaps the most notable aspect of the collaboration is the FDA's amenability to allowing Avanir to proceed into phase IIa with limited phase I data, referencing data from the predecessor product. We believe this speaks to the FDA's comfort with deuteration as a technology and could suggest that future drugs coming out of Concert's platform could also have more expedited development paths.

**Exhibit 22. Summary of AVNR partnership terms**

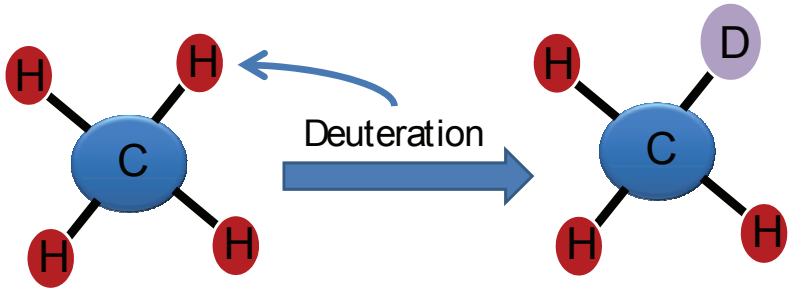
| | |
|---|---|
| **Upfront** | $2M |
| **Potential milestones** | $209M |
| **Royalties** | mid-single/low- double digits below 20% |

Source: Company reports and Wells Fargo Securities, LLC

## Deuteration Technology

**Concert's core technology platform is based on deuterium chemistry.** Deuterium (D) is a naturally occurring isotope of hydrogen (aka, heavy hydrogen), which, when incorporated into compounds selectively, has the potential to alter PK and metabolism without influencing pharmacology. Though other companies, both large (e.g., Merck, Pfizer) and small (e.g., Auspex, Deuteria), have also explored deuterium substitution, Concert is the only company we believe to be fundamentally founded based on the chemistry, which we believe puts it in a leadership position with this technology.

**Exhibit 23. Illustration of deuterium substitution**




Source: Wells Fargo Securities, LLC

**Deuteration, or deuterium substitution, has the potential to confer several advantages.** A hydrogen atom contains one proton and one electron, whereas deuterium, in addition to an equal number of protons and electrons as hydrogen, contains a neutron, making it twice as "heavy" as hydrogen. This leads to a stronger chemical bond with carbon (D-C) compared to hydrogen (H-C). As such, deuterium replacement can fundamentally alter metabolism of drugs, such as via the CYP450 path. This can improve half-life, bioavailability, and metabolic profile, offering several benefits:

- Improve administration/convenience of existing compound, to enhance life cycle: Jazz's Xyrem, which is taken inconveniently twice at night with a four-hour interval; deuterated sodium oxybate is intended to achieve more favorable bioavailability.
- Enable viable development of compounds with interesting properties, but lacking sufficient drug-like characteristics: Deuteration of Merck's '417, which had favorable subtype GABA selectivity, but poor exposure.
- Augment safety profile: Avanir's dextromethorphan, which is metabolized by CYP2D6 and requires co-administration of quinidine to block the enzyme, can be deuterated to enhance bioavailability via increasing resistance to CYP2D6, ultimately lowering required dose of quinidine and potential side effects associated with that component.

**Concert's primary differentiation stems from its ability to determine and execute on optimal deuteration patterns.** Though the concept of D substitution is relatively straightforward, predicting the effects is far from obvious. Careful attention must be paid to selecting both the compounds to deuterate and site of the chemical modifications, in order to generate results harboring clinically meaningful improvements. For example, by slowing down metabolism via one pathway, one can often get "metabolic switching" or diversion to another compensatory pathway, which mitigates any changes. In addition, animal models are not always predictive of PK/metabolic behavior in humans. We believe Concert's years of developing fundamental analytical chemistry around these processes, as well as the high-throughput analytical tools to distinguish between effects of subtle differences in deuteration patterns, is what positions the company best to be a leader in the field of D drug discovery. Indeed, based on our discussions with experts, we believe that while a concept had been experimented with for some time, it was only after Concert began to report preclinical metabolic findings that those in the field started to believe practical application of the technology could be viable. We believe this concept of "non-obviousness" fostered by the company's expertise also helps confer patentability of its drugs.

**We believe the deuterium-based chemistry platform will provide a fertile foundation for long-term pipeline sustainability with drugs that can potentially be moved rapidly through the clinic.** Concert has already synthesized more than 100 compounds in a variety of different disease areas and entered about 5-10 into human clinical trials; a few examples are listed in Exhibit 24.

**Exhibit 24. Deuterated analogs of marketed drugs explored, some clinically, by Concert**

| |
|---|
| D-ivacaftor (Kalydeco) |
| D-lenalidomide (Revlimid) |
| D-praziquantel (Biltricide) |
| D-atazanavir (Reyataz) |
| D-boceprevir (Victrelis) |
| D-ibrutinib (Pharmacyclics) |
| D-ruxolitinib (Jakafi) |
| D-paroxetine (Paxil) |

Source: Company reports and Wells Fargo Securities, LLC

We believe the platform is capable of producing even more drugs than Concert has the resources to put through the clinic. This could enable Concert to be selective about which compounds make the most sense for the company to develop on its own, as opposed to out-licensing to generate non-dilutive cash. In addition, based on our discussions with experts and evidenced by FDA's allowance of Avanir to reference some preclinical data, we believe that since these deuterated compounds' pharmacological/clinical profiles are more predictable than typical small molecule development and regulators might allow less arduous development path in certain cases, the route to market may be relatively quick.

**Intellectual Property**

**We believe CNCE holds a strong IP portfolio on deuterated drug candidates, not only for its pipeline products, but also for many of the known marketed drugs with large commercial opportunities (e.g., ibrutinib, Kalydeco, ruxolitinib, etc.).** Based on expert discussions, we believe Concert's platform's strength stems from unanticipated effects of deuteration uncovered only upon experimentation conducted by Concert's scientist and thus, helping against the obvious objection from the patent office. We believe in addition to the IP, Concert's know-how, trade secrets, manufacturing, and sourcing of chemical intermediates all contribute to a high bar set against potential competitors. Lead program '354 has composition of matter protection through 2029, and our checks indicated that a deuterated form of MRK's '417 had not been previously patented. Similarly, the differentiated deuterated patterns in other products and the corresponding favorable PK/PD properties likely confer these programs with IP protection that should help them withstand challenges in the future. While many companies now incorporate deuteration as a patent strategy, it is yet unclear how aggressively they invest in this strategy as it involves a thorough "reduction to practice" commitment in order to be granted the patent and/or withstand future challenges. We believe Concert's platform could overcome potential obviousness/blocking claims by leveraging its systematic approach to finding unexpected properties in the molecules of interest. Issued composition of matter patents and method-of-use patents are summarized in the following exhibit.

**Exhibit 25. Issued composition of matter patents and method-of-use patents**

| Product | Patent | Est. Exp. | Comment |
|---|---|---|---|
| CTP-354 | 8,003,646 | 2029 | Composition of matter |
| | 8,399,467 | 2029 | Method of use |
| CTP-499 | 8,263,601 | 2029 | Composition of matter |
| CTP-786 (Avanir) | 7,973,049 | 2028* | Composition of matter |
| | 8,541,436 | 2028 | Method of treatment |
| | 8,188,110 | 2028 | Method of treatment |
| CTP-386 (Jazz) | 8,461,197 | 2030 | Composition of matter |

Source: Company reports, USPTO, and Wells Fargo Securites, LLC

*2030 with patent term extension

## Balance Sheet

| | 12/31/2011 | 12/31/2012 | 9/30/2013 | Pro Forma 9/30/2013 |
|---|---|---|---|---|
| **Assets:** | | | | |
| Current assets: | | | | |
| Cash and cash equivalents | $22,949 | $7,490 | $18,612 | $18,612 |
| Short-term investments, available for sale | $19,705 | $20,067 | $22,705 | $22,705 |
| Interest receivable | $128 | $102 | $115 | $115 |
| Accounts receivable | $500 | $13 | $164 | $164 |
| Prepaid expenses and other current | $853 | $1,178 | $1,305 | $1,305 |
| Total current assets | $44,135 | $28,850 | $42,901 | $42,901 |
| Property and equipment, net | $4,438 | $3,454 | $2,591 | $2,591 |
| Long-term investment | | | $1,256 | $1,256 |
| Restricted cash | $706 | $706 | $706 | $706 |
| Other assets | $124 | $119 | $1,515 | $1,515 |
| Total assets | $49,403 | $33,129 | $48,969 | $48,969 |
| **Liabilities & Shareholders' Equity:** | | | | |
| Current liabilities: | | | | |
| Accounts payable | $1,576 | $813 | $953 | $953 |
| Accrued expenses and other liabilities | $1,472 | $1,953 | $2,918 | $2,918 |
| Deferred revenue, current portion | $6,894 | | $3,997 | $3,997 |
| Leasehold improvement loan, current | $332 | $332 | $332 | $332 |
| Loans payable, net of discount | | $4,812 | $7,651 | $7,651 |
| Total current liabilities | $10,274 | $7,910 | $15,851 | $15,851 |
| Deferred revenue, net of current portion | $4,128 | $2,750 | $16,551 | $16,551 |
| Leasehold improvement loan, net of current | $913 | $581 | $332 | $332 |
| Deferred lease incentive, net of current | $1,411 | $898 | $513 | $513 |
| Deferred rent, net of current portion | $632 | $451 | $277 | $277 |
| Warrant to purchase redeemable securities | $168 | $459 | $489 | |
| Loan payable, net of current portion and | $7,135 | $14,919 | $9,120 | $9,120 |
| Total liabilities | $24,661 | $27,968 | $43,133 | $42,644 |
| Commitments | | | | |
| Redeemable convertible preferred stock | $111,460 | $111,848 | $112,144 | |
| Stockholders' (deficit) equity: | | | | |
| Common stock, $0.001 par value per share; 83,716,667 shares authorized; 1,290,238 shares issued and outstanding at December 31, 2011 and 2012 and 1,295,191 shares issued and outstanding at September 30, 2013 (unaudited); 11,215,012 shares issued and outstanding pro forma (unaudited) | $1 | $1 | $1 | 11 |
| Additional paid-in capital | $409 | $889 | $1,406 | $114,029 |
| Accumulated other comprehensive income | $9 | $4 | $7 | $7 |
| Accumulated deficit | ($87,137) | ($107,581) | ($107,722) | ($107,722) |
| **Total stockholders' (deficit) equity** | ($86,718) | ($106,687) | ($106,308) | $6,325 |
| **Total liabilities, redeemable convertible preferred stock and stockholders' (deficit) equity** | $49,403 | $33,129 | $48,969 | $48,969 |

Source: Concert Pharmaceuticals S-1, filed January 2014 and Wells Fargo Securities, LLC
Note: in 000's USD

**Concert Pharma (CNCE)**
Statement of Operations (Income Statement)

| | 2012A | 2013E | 1Q | 2Q | 3Q | 4Q | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E | 2022E | 2023E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Revenues (1) | | | | | | | | | | | | | | | | |
| *Revenues from CTP-354* | | | | | | | | | | | | | $48,920 | $102,009 | $251,076 | $432,811 |
| *Royalties from sales of CTP-499* | | | | | | | | | | | $15,202 | $33,127 | $54,922 | $79,442 | $106,951 | $137,737 |
| *Royalties from sales of AVP-786* | | | | | | | | | | | | | | $10,032 | $23,732 | $41,304 |
| *Royalties from sales of JZP-386* | | | | | | | | | | | | | | | $24,733 | $62,972 |
| Milestones | $1,500 | $2,000 | $0 | $2,000 | $0 | $0 | $2,000 | $14,000 | $30,000 | $15,000 | $34,000 | $45,000 | $0 | $48,000 | $72,000 | $15,000 |
| License and research and development revenue | $11,349 | $25,895 | $880 | $880 | $880 | $880 | $3,520 | $8,520 | $12,520 | $12,520 | $12,520 | $9,000 | $9,000 | $9,000 | $9,000 | $9,000 |
| **Total revenues, net** | **$12,849** | **$27,895** | **$880** | **$2,880** | **$880** | **$880** | **$5,520** | **$22,520** | **$42,520** | **$27,520** | **$61,722** | **$87,127** | **$112,843** | **$248,483** | **$487,493** | **$698,824** |
| Expenses | | | | | | | | | | | | | | | | |
| Cost of goods sold | | | | | | | | | | | | | $4,892 | $9,669 | $15,536 | $22,622 |
| Research and development | $24,193 | $22,460 | $6,500 | $7,000 | $7,100 | $7,200 | $27,800 | $28,912 | $30,068 | $31,271 | $32,522 | $33,823 | $35,176 | $36,583 | $38,046 | $39,568 |
| Selling, general and administrative | $7,266 | $8,666 | $2,600 | $2,800 | $2,850 | $2,900 | $11,150 | $12,265 | $12,756 | $13,266 | $15,919 | $39,797 | $67,656 | $101,484 | $126,854 | $139,540 |
| **Total operating expenses** | **$31,459** | **$31,126** | **$9,100** | **$9,800** | **$9,950** | **$10,100** | **$38,950** | **$41,177** | **$42,824** | **$44,537** | **$48,441** | **$73,620** | **$107,724** | **$147,735** | **$180,437** | **$201,730** |
| **Operating Income** | **($18,610)** | **($3,231)** | **($8,220)** | **($6,920)** | **($9,070)** | **($9,220)** | **($33,430)** | **($18,657.00)** | **($304)** | **($17,017)** | **$13,280** | **$13,507** | **$5,119** | **$100,748** | **$307,056** | **$497,094** |
| Investment income | $22 | $29 | $13 | $22 | $20 | $17 | $71 | $74 | $99 | $98 | $82 | $83 | $108 | $174 | $354 | $708 |
| Interest and other expense | ($1,856) | ($1,688) | ($322) | ($265) | ($208) | ($149) | ($943) | ($295) | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| CTP-499 commercialization payment to GSK | | | | | | | | | | | ($2,750) | | | | | |
| **(Loss) income before benefit from income taxes** | **($20,444)** | **($4,890)** | **($8,528)** | **($7,163)** | **($9,258)** | **($9,352)** | **($34,301)** | **($18,878)** | **($205)** | **($16,919)** | **$10,613** | **$13,590** | **$5,227** | **$100,923** | **$307,410** | **$497,802** |
| Benefit (expense) from income taxes | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | ($212) | ($272) | ($105) | ($6,055) | ($24,593) | ($54,758) |
| **Net (loss) income** | **($20,444)** | **($4,890)** | **($8,528)** | **($7,163)** | **($9,258)** | **($9,352)** | **($34,301)** | **($18,878)** | **($205)** | **($16,919)** | **$10,400** | **$13,318** | **$5,123** | **$94,867** | **$282,818** | **$443,044** |
| Accretion on redeemable convertible preferred stock | ($388) | ($400) | **($100)** | **($100)** | **($100)** | **($100)** | ($400) | ($300) | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **Net loss applicable to common shareholders** | **($20,832)** | **($5,290)** | **($8,628)** | **($7,263)** | **($9,358)** | **($9,452)** | **($34,701)** | **($19,178)** | **($205)** | **($16,919)** | **$10,400** | **$13,318** | **$5,123** | **$94,867** | **$282,818** | **$443,044** |
| **Earnings per share (EPS)** | **($2.86)** | **($0.64)** | **($0.64)** | **($0.41)** | **($0.52)** | **($0.52)** | **($2.05)** | **($1.02)** | **($0.01)** | **($0.84)** | **$0.42** | **$0.52** | **$0.19** | **$3.36** | **$9.80** | **$15.03** |
| Shares Outstanding (Basic) | 7,290 | 8,276 | 13,435 | 17,868 | 18,068 | 18,268 | 16,909 | 18,868 | 19,468 | 20,068 | 20,668 | 21,268 | 23,534 | 24,134 | 24,734 | 25,334 |
| Shares Outstanding (Diluted) | 7,290 | 8,276 | 17,571 | 22,004 | 22,204 | 22,404 | 21,045 | 23,004 | 23,604 | 24,204 | 24,804 | 25,404 | 27,670 | 28,270 | 28,870 | 29,470 |

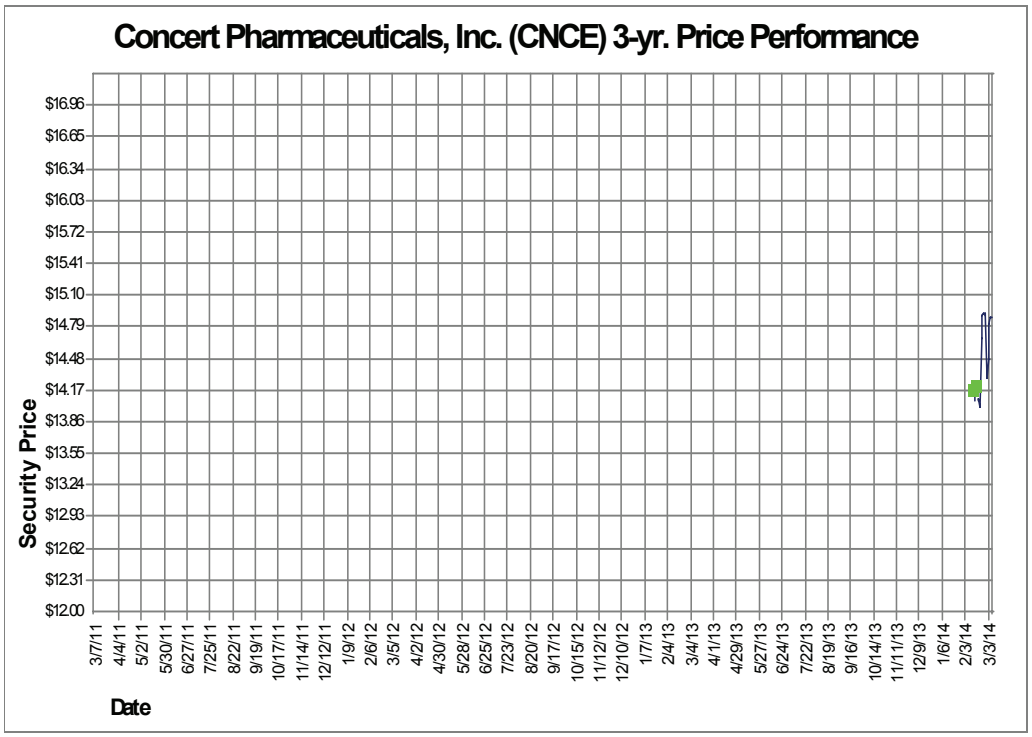
Source: Company reports and Wells Fargo Securities, LLC

Note: We do not provide estimates of 2015 quarterly EPS at this point.

Note: In 000's $, except per share amounts; FY ends 12/31

(1) Not probability weighted

# Required Disclosures




| | Date | Publication Price ($) | Rating Code | Val. Rng. Low | Val. Rng. High | Close Price ($) |
|---|---|---|---|---|---|---|
| ❐ | 2/13/2014 | | IPO at $14.00 | | | |

Source: Wells Fargo Securities, LLC estimates and Reuters data

**Symbol Key**

| | | | |
|---|---|---|---|
| ▼ | Rating Downgrade | ◆ | Initiation, Resumption, Drop or Suspend |
| ▲ | Rating Upgrade | ■ | Analyst Change |
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**Rating Code Key**

| | | | |
|---|---|---|---|
| 1 | Outperform/Buy | SR | Suspended |
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## *TECHNOLOGY & SERVICES*

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