Initiation of Coverage

Concert Pharmaceuticals

The Deuteration Abides: Initiating Concert at Buy

Initiating CNCE coverage with a Buy and $25 Price Target

Concert Pharmaceuticals is a clinical-stage biotech company that we believe is strongly positioned to produce deuterium-based new drug compounds as well as analogues of well-characterized drugs with improved tolerability, less frequent dosing, and reduced drug interactions. The company is currently developing its two wholly-owned assets, CTP-354 (for spasticity associated with multiple sclerosis and spinal cord injury) and CTP-499 (for diabetic kidney disease). In addition, we believe Concert's partnerships with Jazz, Avanir, and in particular Celgene, could be significant value creators.

The go-to company in deuterium substitution

Key tenets of our Buy thesis: [1] Concert has extraordinary expertise in medicinal chemistry and deuterium modification, and in our view is a well-positioned leader in an art that has a high barrier to entry. To us, the supporting evidence is its high-quality partnerships, and our checks on the highly credible management team with a track record of invention. [2] Neither of its two wholly-owned product candidates are de-risked, but if successful, each has over $1bn potential. [3] Comparable valuations and revenue potential suggest significant upside potential. Its catalyst path to value creation is well-defined, with incremental newsflow in 2014 but key clinical data in 2015.

Overcoming limitations of well-characterized drugs of strategic importance

Although the favorable effects of deuterium on pharmacokinetic (PK) properties of drug candidates have been known for over 50 years, currently there are no approved drugs containing deuterium. However, we believe there is sufficient evidence that on a case-by-case basis, the technology not only can improve validated drugs, but also can overcome problematic PK and enable the advancement of candidates with otherwise promising pharmacologic activity (example, CPT-354). Taken together, we believe Concert's expertise, mastery of deuterium modification, products and platform will increase in strategic value as its programs and those of its partners are advanced.

Valuation: $25 Price Target by SOTP supported by DCF

Our PT assumes 10x multiples on royalty revenues and 3x on wholly-owned programs.

Equities

Americas
Biotechnology

12-month rating	**Buy** *Prior: Not Rated*
12m price target	**US$25.00** *Prior: -*
Price	**US$14.88**

RIC: CNCE.O **BBG:** CNCE US

Trading data and key metrics

52-wk range	US$14.97-0.00
Market cap.	US$0.26bn
Shares o/s	17.2m (COM)
Free float	35%
Avg. daily volume ('000)	10
Avg. daily value (m)	US$0.2
Common s/h equity (12/13E)	US$0.01bn
P/BV (12/13E)	28.6x
Net debt / EBITDA (12/13E)	NM

EPS (UBS, diluted) (US$)

	12/13E			
	From	To	% ch	Cons.
Q1	-	-	-	-
Q2	-	-	-	-
Q3	-	-	-	-
Q4E	-	-	-	-
12/13E	-	(0.04)	-	-
12/14E	-	0.28	-	-
12/15E	-	0.22	-	-

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Highlights (US$m)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Revenues	-	19	13	32	44	55	82	105
EBIT (UBS)	-	(11)	(19)	2	7	6	4	(3)
Net earnings (UBS)	-	(11)	(22)	0	6	5	2	(5)
EPS (UBS, diluted) (US$)	-	(1.56)	(2.00)	(0.04)	0.28	0.22	0.10	(0.27)
DPS (US$)	-	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Net (debt) / cash	-	23	7	19	94	100	115	123

Profitability/valuation	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
EBIT margin %	-	-58.3	-144.8	4.9	16.6	11.2	4.5	-2.8
ROIC (EBIT) %	-	-	>500	(19.1)	(88.0)	<-500	144.4	(115.7)
EV/EBITDA (core) x	-	-	-	94.3	23.5	21.4	29.3	-95.3
P/E (UBS, diluted) x	-	-	-	NM	53.4	68.3	NM	(56.0)
Equity FCF (UBS) yield %	-	-	-	7.1	2.0	3.5	3.7	1.2
Net dividend yield %	-	-	-	0.0	0.0	0.0	0.0	0.0

Source: Company accounts, Thomson Reuters, UBS estimates. Metrics marked as (UBS) have had analyst adjustments applied. Valuations: based on an average share price that year, (E): based on a share price of US$14.88 on 07 Mar 2014 19:43 EST

Investment Thesis

Concert Pharma

12-month rating	**Buy**
12m price target	**US$25.00**

Investment case

The key tenets of our Buy rating on CNCE are: [1] Concert has extraordinary expertise in medicinal chemistry and deuterium modification, and in our view is a well-positioned leader in an art that has a high barrier to entry. To us, the supporting evidence is its high-quality partnerships, and our checks on the highly credible management team with a track record of invention. [2] Neither of its two wholly-owned product candidates are de-risked, but if successful, each has over $1bn potential. [3] Comparable valuations and revenue potential suggest significant upside potential. Its catalyst path to value creation is well-defined, with incremental newsflow in 2014 but key clinical data in 2015.

Upside scenario

Our upside scenario $48 reflects a higher probability of success for the two wholly-owned compounds. We assume 30% for CTP-354 in MI and SCI, and 40% for CTP-499 in CKD.

Downside scenario

Our downside scenario $8 assumes a failure of CTP-345 in MS and SCI. The downside scenario is likely to change in value if partners Celgene, Jazz, or Avanir advance (or not advance) programs, as the partnerships are keys to determining the valuation support for CNCE.

Upcoming catalysts

[1] ph1 multiple-dose data of '354 in 2H14; [2] final data from open-label extension of ph2 trial of '499 in 2014; [3] feedback from end-of-ph2 meeting with FDA in 2H14; [4] data from Jazz' ph1 trial in 2014; [5] ph2 data of '354 in spasticity in 2015; [6] potential partnership of '499 2014-15.

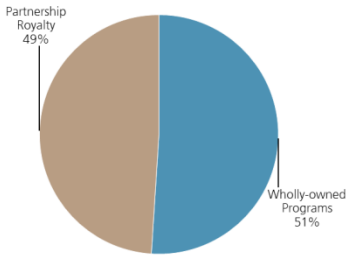
Business description

Concert Pharmaceuticals is a clinical-stage company that applies its knowledge of deuterium chemistry to develop novel small molecule drugs using its Deuterated Chemical Entity (DCE) Platform. Among its wholly-owned assets, the company is currently developing CTP-354 for spasticity associated with multiple sclerosis/spinal cord injury and CTP-499 for diabetic kidney disease. In addition, the company is developing product candidates in its partnerships with Celgene, Jazz Pharmaceuticals, and Avanir.

Industry outlook

While we expect large cap biotech to continue positive momentum on strong earnings growth, the smid cap universe will continue to be very data-driven and to be tightly correlated to market risk appetite. Many smid-cap names have gotten credit for pipeline optionality during the recent biotech rally, but we believe CNCE can be an outperformer of peers based on organic pipeline development and potential partnering.

Revenues by segment (%)



EBIT by product segment

Segment Revenues ($m)	2017E	2018E	2019E	2020E
Neurology	1	7	29	63
Nephrology	0	4	12	20
Oncology	0	0	1	4
Other License and Milestones	104	141	173	175
Total	105	152	214	261

Source for chart and table: UBS

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Overview

We are initiating coverage of Concert Pharmaceuticals (CNCE) with a Buy rating and a $25 price target. Concert is a clinical-stage biotech company with an underlying platform to deliver significant value by substituting hydrogen atoms for deuterium atoms in drug candidates, resulting in different pharmacokinetic profiles that could result in improved tolerability, less frequent dosing, and reduced drug interactions. Each of the wholly-owned product candidates (CTP-354 for spasticity associated with multiple sclerosis or spinal cord injury, and CTP-499 for diabetic kidney disease), are being developed to serve markets of over $1bn, and the platform has already yielded partnerships with Avanir, Celgene, and Jazz Pharmaceuticals that could be significant value creators. We believe that a catalyst path to value creation is well-defined, with studies across the wholly-owned and partnered programs beginning or reporting data over the next 12-18 months. Although the effects of deuterium on pharmacodynamics properties have been known for over 50 years, there currently are no approved drugs containing deuterium. However, Concert has best-in-class expertise in this field with a highly credible management team to bring a deuterated analogue to market. We believe that comparable valuations suggest significant upside potential given the combination of wholly-owned product candidates and partnered programs, and on a risk-adjusted basis we believe the stock could reach $25 over the next year.

We are initiating CNCE with a Buy rating and are establishing a $25 Price Target

Key investment points

1. Concert has a platform that should deliver significant value

The company's platform substitutes hydrogen with deuterium on drug candidates' carbon backbone. Because the carbon-deuterium covalent bond requires about eight times more energy to break than the carbon-hydrogen bond, deuterium substitution results in different pharmacokinetic profiles from hydrogen analogues, potentially resulting in improved tolerability, less frequent dosing, and reduced drug interactions. Significant benefits have been seen in other drugs after modifying pharmacokinetics to reduce blood level fluctuations, including extended release Ampyra, Effexor XR, and Gralise. In addition to a reduction in the formation of toxic metabolites, substitution of deuterium for hydrogen has not been seen to alter the underlying pharmacology or intrinsic biologic activity of a drug, resulting in retained potency and selectivity.

2. Their wholly-owned product candidates, if successful, each have peak sales potential of over $1bn

Concert is currently developing two wholly-owned product candidates: CTP-354 for spasticity associated with multiple sclerosis and spasticity associated with spinal cord injury, and CTP-499 for diabetic kidney disease.

CPT-354. Spasticity is a condition of involuntary muscle contraction, often caused by damage to the part of the brain or spinal cord that controls voluntary movement. In the U.S., we estimate that about a third of the 400,000 MS patients are currently affected by moderate to severe spasticity, and 100,000 of the 270,000 patients with SCI experience spasticity that requires treatment.

We assign a 15% probability of success for CPT-354 *(subject to significant change with ph2 data in 2015e)*

In 2019, '354 would address a multi-billion dollar market with ~158,000 MS and ~116,000 SCI patients at a launch price of $25,000. We model annual sales of '354 exceeding $1bn in its fifth year of launch (2023e).

CPT-499. Diabetic kidney disease refers to type 2 diabetes (T2D) patients having chronic kidney disease (CKD) and macroalbuminuria (larger amounts of protein in the urine), and CTP-499 is being developed to slow the progression of CKD in these patients. We estimate that 925,000 of the 23 million patients with T2D in the U.S. have CKD and macroalbuminuria.

We assign a 20% probability of success for CPT-499 *(subject to change based on end of ph2 meeting in 2014e)*

In 2018, we assume '499 will launch into a multi-billion dollar market in diabetic kidney disease, with ~536,000 patients at a launch price of $10,000. On an unrisk-adjusted basis, we model annual sales of '499 exceeding $1bn in its seventh year of launch (2024e).

3. The platform has already yielded multiple partnerships

In addition to their two wholly-owned compounds, Concert has partnerships with Celgene, Jazz Pharmaceuticals, and Avanir, for the development of multiple product candidates. We believe these partnerships, which total potential milestones of $1.7b, serve three purposes: they are a source of non-dilutive finance, they illustrate strategic value, and validate the platform.

Avanir as validation. Concert is developing a deuterated dextromethorphan with low-dose quinidine, AVP-786, with Avanir to treat neurologic and psychiatric disorders. AVP-786 is an analogue to Avanir's Nuedexta, and while quinidine is required to slow the rapid metabolism of dextromethorphan, lower doses of quinidine are desired as it can cause heart rhythm changes. Concert is eligible for up to $166m in milestones in addition to tiered royalties. Avanir is planning to advance AVP-786 into phase-2 in 2H14.

We view the Avanir partnership as a proof-of-concept, but appears to be less strategically and financially important

Celgene the most valuable partnership. The company is developing on up to four compounds with Celgene for treating **cancer** or **inflammation** with deuterium-substituted compounds. Concert is initially focusing on developing CTP-730 to treat inflammatory diseases, with a phase-1 beginning this year. Based on pre-partnership disclosures, we believe CPT-730 to be a deuterated **Otezla** (apremilast). Recall Otezla is a twice-daily drug and has a few tolerability issues while onboarding patients. We also are aware of a deuterated **Revlimid** (lenalidomide) program, for which data were presented at ASH 2012. Across the four potential compounds, Concert is eligible for approximately $1.4bn in milestones in addition to tiered royalties.

We view the Celgene partnership as Concert's most valuable (strategically and financially)

Also a nice opportunity for Jazz. In its partnership with Jazz, Concert is developing JZP-386, a deuterated analogue of sodium oxybate. Sodium oxybate is the active ingredient in Jazz's Xyrem, which is used to treat symptoms of narcolepsy, specifically cataplexy and excessive daytime sleepiness. JZP-386 has shown a prolonged pharmacokinetic profile and reduced variability in preclinical in vivo studies. The phase-1 study is expected to begin and yield initial data in 2014, and Concert is eligible for up to $113m in milestones in addition to tiered royalties.

4. A catalyst path to value creation is well-defined

Over the next 12-18 months, data for both wholly-owned and partnered programs should drive meaningful appreciation and valuation more in-line with comps. For '354, multiple dose data from the phase-1 study is expected in 2H14, while data from the phase-2 studies in MS and SCI (expected to begin in 2H14) should report

in 2015. For '499, final data from the open label extension of the phase-2 trial is expected this year. As previously mentioned, Avanir is beginning the phase-2 study of AVP-786 in 2H14, a phase-1 study for Celgene-partnered CTP-730 is expected to begin this year, and Jazz will begin and report initial data from the phase-1 study of JZP-386 this year.

5. Past experience with deuterium suggests high barrier to entry

Although the effects of deuterium on pharmacodynamic properties were described over 50 years ago, there currently is no approved drug containing deuterium. Companies such as Auspex Pharmaceuticals and DeuteRx (a spin-off of Deuteria Pharmaceuticals, which was acquired by Celgene) are using deuterium substitution, but based on expert consults, we believe Concert's has best-in class capability in this select field. In addition to the company's expertise in deuterium chemistry and manufacturing, Concert holds over 100 patents worldwide, including 50 in the U.S. A summary of U.S. patents for the wholly-owned and partnered programs is shown in Figure 1.

Figure 1: Summary of Concert's US patent coverage for its product candidates

Product	Patent Expiration	Type
CTP-354	2029	Composition of matter; compositions and methods
CTP-499	2029	Composition of matter
AVP-786	2028-2030	Composition of matter; methods of use
Celgene collaboration	2030	Composition of matter
JZP-386	2030	Composition of matter; methods of use for treating certain diseases and disorders

Source: Company reports, UBS research

6. The management team is highly credible

Management has worked on 12 drugs that have been approved by the FDA

The Concert team has substantial expertise in drug development, having been involved in the R&D or approval of 12 drugs. Before founding Concert, Dr. Roger Tung was Vice President of Drug Discovery at Vertex Pharmaceuticals. While at Vertex, he became a co-inventor of amprenavir and fosamprenavir, approved for treating HIV, and he oversaw discovery of Kalydeco (ivacaftor) for cystic fibrosis and Incivek (telaprevir) for hepatitis C.

7. Comps and revenue potential suggests significant upside potential in CNCE shares

With regards to its pipeline portfolio, we believe Concert represents the best of both worlds with wholly-owned compounds and partnered programs. On its platform, we believe the closest comps are antibody-drug conjugates (ADC). By both DCF and sum-of-the-parts, we arrive at net present values that are higher than Concert's market cap. In addition, looking at comps of companies with phase-2 assets or later as well as partnerships, the mean market cap of the three companies we found is $794m. Both comps and fundamental evaluation suggest significant upside potential.

Forthcoming Catalysts

Concert has two wholly-owned clinical assets, CTP-354 and CTP-499, as well as three main partnered programs with Avanir, Celgene, and Jazz Pharmaceuticals. Final top-line 48-week results for the CTP-499 phase-2 are expected in 1H14. Concert expects to initiate two phase-2 studies for CTP-354 in 2H14, one for multiple sclerosis and one for spinal cord injury (SCI).

Specific catalysts for the pipeline are listed in Figure 2.

Figure 2: Upcoming catalysts – Concert Pharmaceuticals

Key Events	Timeline	Potential Impact
CTP-354: Phase 1 multiple dose data	2H14	++
CTP-354: Initiate Phase 2 program in spasticity in MS and SCI	2H14	+
CTP-499: Complete and report final data from open label extension of Phase 2 trial	2014	+
CTP-499: Feedback from end-of-Phase 2 meeting with FDA	2H14	++
CTP-499: Potential partnering?	2014-2015?	+++?
Avanir: Initiate Phase 2 trial in treatment-resistant major depressive disorder	2H14	+
Jazz: Data from Phase 1 trial	2H14	+
Celgene: Initiate Phase 1 CTP-730 trials	2014	+
CTP-354: Phase 2 data in spasticity in MS and SCI	2015	++++
Partner data: Phase 1 data from Celgene	2015	++

Note: Impact scale ++++ highest to + lowest
Source: Company reports and UBS research

Valuation

We reach our $25 price target by SOTP supported by DCF. Our revenue estimates include sales from CTP-354 and royalty / milestones from partnership programs. We assume CTP-354 will remain wholly-owned, whereas CTP-499 will be partnered. Our model suggests CTP-354 will achieve over $500m US sales in 2023, which represents only 15% of the total addressable MS spasticity market and 2% of the spinal cord injury spasticity market. The projected sales are further adjusted with a 15% probability of success. Our DCF is driven off the risk-adjusted sales estimates, with a 13.5% discount rate applied to future cash flows. Our price target is DCF-based but also supported by applying a multiple-based sum-of-the-parts analysis. Figure 3 summarizes the results of the two valuation methods.

Our price target incorporates a 13.5% discount rate. With shares trading at a market cap of $249m, the current valuation implies a heavily risk-adjusted technology outlook on the Concert program. While a 10-12% probability of success (i.e. FDA approval) is generally in line with similarly-staged assets in neurology, we believe that the underlying platform, along with the company's expertise in deuterium substitution, necessitate a higher probability of success (POS) than the market implies.

We risk-adjusted each of the programs. We risk-adjusted U.S. revenues from '354 with a 15% probability of success. For '499, we assumed a 20% probability of success and a double-digit royalty from an upcoming partner since management made their intentions clear for partnering this asset beginning with the phase-3 trials. For each of the partnered programs, we estimated a risk-adjusted milestone payment by taking consensus worldwide sales for each hydrogen-based compound

and discounting by 25% to reach the expected sales for the corresponding deuterium analogue. From the expected sales, we estimate the royalty that Concert will receive from the partner, and adjust based on a probability of success (20% for CTP-730 and JZP-386, 50% for AVP-786).

Figure 3: CNCE valuation by DCF and sum-of-the-parts: We launch with a $25 PT

Product	Risk-Adj. Revenue	Year	Multiple	Discount Rate	NPV	NPV (Per Share)	% of Value
CTP-354 sales - US	133	2022	3.0	13.5%	145	$6.85	27%
CTP-354 royalties on Ex-US sales	10	2022	10.0	13.5%	35	$1.64	6%
Total CTP-354	142				179	$8.48	34%
CTP-499 Royalty Revenue	39	2022	10.0	13.5%	142	$6.72	27%
JAZZ Royalty Revenue	15	2022	10.0	13.5%	56	$2.65	11%
AVNR Royalty Revenue	15	2022	10.0	13.5%	55	$2.61	10%
CELG Royalty Revenue	16	2022	10.0	13.5%	57	$2.69	11%
Total Royalty Revenue	85				310	$14.67	58%
Net cash					45	$2.12	8%
Total					533	$25.28	100%

Valuation	DCF	Sum-of-the-parts	Average
NPV	$516m	$537m	$527m
Per share	$24.46	$25.44	$24.95

Source: UBS research

Comparable valuation suggests significant upside. Figure 4 provides the comparable valuations for companies that have platforms or are in phase-2. Of these, only three have proprietary programs in phase-2 assets or later, as well as partnerships: Acceleron Pharma, Portola Pharmaceuticals, and KaloBios Pharmaceuticals. The mean market cap of these three companies is $794m (range $84m to $1,435m). At Concert's current market cap, the comps suggest significant upside.

Figure 4: Comparable valuations

Company	Ticker	Last price ($)	Market cap ($M)	Enterprise value ($M)	Cash & short term inv ($M)	Last 12-mo NI ($M)	Debt ($M)	2014 consensus sales ($M)
Platform companies								
Halozyme Therapeutics, Inc.	HALO	$13.81	1,574	1,523	100	(83)	50	294
Epizyme, Inc.	EPZM	$29.06	826	792	33	(3)	0	100
Agios Pharmaceuticals, Inc.	AGIO	$30.14	935	755	179	(32)	0	67
Merrimack Pharmaceuticals, Inc.	MACK	$5.17	528	518	50	(131)	40	283
Verastem, Inc.	VSTM	$13.23	338	206	132	(38)	0	16
Regulus Therapeutics Inc.	RGLS	$11.55	475	447	38	(19)	10	36
Five Prime Therapeutics, Inc.	FPRX	$13.78	221	170	51	NA	0	52
mean			**699**	**630**				
median			**528**	**518**				
Phase-2/Pipeline/Market Comps								
Acceleron Pharma Inc	*XLRN*	*$48.30*	*1,485*	*1,442*	*65*	*(22)*	*22*	*88*
Portola Pharmaceuticals, Inc.	*PTLA*	*$23.14*	*813*	*682*	*131*	*(83)*	*0*	*233*
Lexicon Pharmaceuticals, Inc.	LXRX	$1.75	899	640	282	(104)	23	99
Endocyte, Inc.	ECYT	$13.07	470	342	128	(18)	0	106
Chemocentryx, Inc.	CCXI	$7.31	312	223	89	(39)	1	1
Xenoport	XNPT	$6.09	291	196	94	(86)	0	122
Alcobra Ltd.	ADHD	$23.10	257	257	1	(11)	1	54
Esperion Therapeutics, Inc.	ESPR	$15.85	243	262	2	(19)	20	0
BIND Therapeutics, Inc.	BIND	$13.48	213	190	26	(25)	3	32
Conatus Pharmaceuticals Inc.	CNAT	$11.31	186	171	17	(13)	1	0
KaloBios Pharmaceuticals, Inc.	*KBIO*	*$3.29*	*84*	*76*	*18*	*(43)*	*10*	*11*
mean			**477**	**407**				
median			**291**	**257**				

Source: UBS research, FactSet

Upside & Downside Scenarios

Upside scenario: $48. Our upside scenario reflects a higher probability of success for the two wholly-owned compounds. We assume 30% for CTP-354 in MI and SCI, and 40% for CTP-499 in CKD.

Downside scenario: $8. Our downside scenario assumes a failure of CTP-345 in MS and SCI. The downside scenario is likely to change in value if partners Celgene, Jazz, or Avanir advance (or not advance) programs, as the partnerships are keys to determining the valuation support for CNCE

Key Risks

We see several risks to our Buy rating on CNCE shares.

- **Clinical risk:** The principle risk is clinical development. Failure of the two lead assets on efficacy and/or safety would represent a delay to commercialization, since CNCE would revert to back-up compounds in earlier stages of development.
- **Regulatory risk:** If Concert completes clinical trials and applies for marketing authorization in the U.S. and EU, it would face risk that the regulatory agencies do not approve the drug candidates.

- **Commercial risks:** We believe the bar for coverage and reimbursement is higher than ever. Concert's approach using deuterated analogues is not entirely unique, and they are not be the only company developing compounds to treat spasticity or type 2 diabetic kidney disease – further competition may or may not materialize. In addition, if the company bring products to the market, generic competitors could challenge their patent estate.
- **Execution risk:** Biotech drug development and translation into commercialization is difficult.

Environmental, Social, and Governance issues

The primary social issues we see affecting biotechnology is that of drug pricing and global access. While providing access to life-saving drugs is a priority for all of the companies, realities of the market are often balanced against perceived/intended social obligations. All of the companies we cover employ compassionate use programs that enable patients to benefit from therapies that are either too costly to afford or are still in clinical development but provide tremendous benefit to the patient, often life-saving.

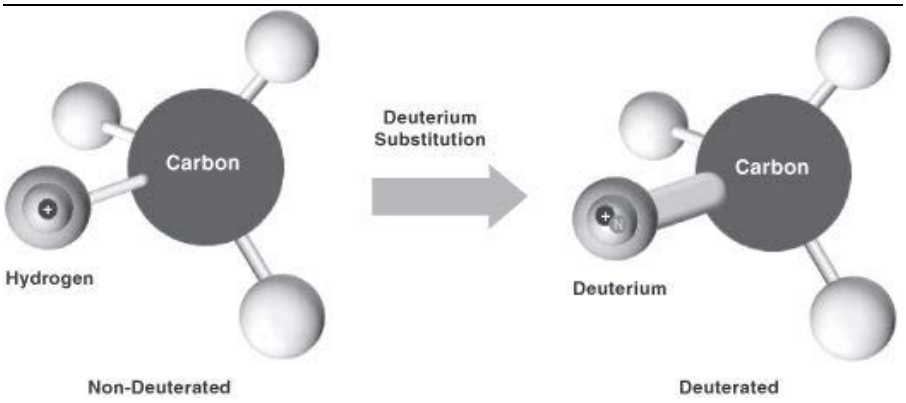
What You Need To Know on Fundamentals

Deuterium substitution

What is deuterium substitution?

Concert's strategy involves selectively replacing hydrogen atoms in oral small-molecule drugs with another isotope of the element: deuterium. Normally, a hydrogen atom consists of just one proton and one electron, but deuterium also has a neutron. This doubles the molecular weight of this 'heavy hydrogen', leading to stronger molecular bonds—and, researchers hope, more stable resulting drugs.

Figure 5: Deuterium substitution



Source: Company reports

Why does deuterium matter?

Deuterium substitution can improve bioavailability while retaining its original biochemical properties. Deuterium-carbon bonds are generally about six to 10 times more stable than the corresponding hydrogencarbon bond. These stronger bonds are more difficult to break, which can slow the rate of bond cleavage [1]. Therefore, deuteration has the potential to affect the biological fate of drugs that are metabolized in ways involving breaking down hydrogen-carbon bonds. It has been reported that deuteration reduced rates of metabolism [2,3]. Meanwhile, deuterium substitution generally has not been seen to change the biological activity of a drug, retaining potency and selectivity when compared to hydrogen-based analogues. Concert has summarized the pharmacological effects of deuteration into three major categories

Deuterium reduces the rate of systemic clearance. Because of a lower rate to break down the deuterium-carbon bonds, the biological half-life of the compound

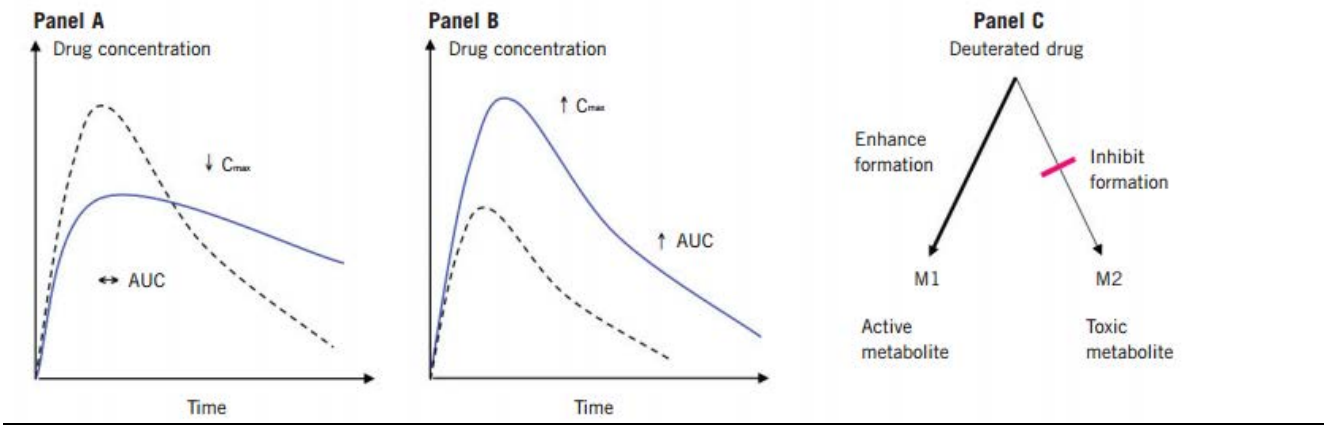
[1] Bell *Chem Soc Rev* 1974
[2] Kushner *Can J Physiol Pharmacol* 1999
[3] Mutlib *Toxicol Appl Pharmacol* 2000

is increased. Potential drug benefits could include a reduction in dosage and the ability to maintain similar systemic exposure with lower peak levels (Cmax) and increased trough levels (Cmin) with the potential to favorably modify the area under the curve (AUC) concentration as well. This could result in a lower incidence of side effects and enhanced efficacy (Figure 6A).

Deuteration increases availability of unmetabolized drug. Deuteration reduces the rates of oxidative degradation of drugs in the gut and liver and thereby results in a larger proportion of unmetabolized drug reaching systemic circulation. In the cases where the rate of systemic clearance is unchanged, this pre-systemic effect could reduce dosing requirements and prevent gastrointestinal irritation that has been related to the amount of dosed compound rather than blood concentration for certain drugs. This would enhance tolerability and the ability to achieve a higher maximum tolerated dose (Figure 6B).

Deuteration enhances formation of metabolites with desirable properties. Many drugs are metabolised in complex patterns, sometimes forming both active and toxic metabolites. By changing the relative rate of metabolism in these pathways, deuteration can shift the balance by reducing formation of toxic metabolites, while increasing formation of desirable active metabolites (Figure 6C).

Figure 6: Pharmacological effects of Drug Deuteration



Source: Company reports

Deuterium has remarkably low toxicity to human. Humans can tolerate high levels of deuterium in body fluids. Acute exposure levels of 15-23% deuterium replacement in whole body plasma have been reported with no evident adverse effects [4].

Where and how to substitute deuterium is the key

Although based on the isotype effects explained above, the concept of improving existing drugs by deuteration might seem to be obvious, it can be difficult and certainly non-obvious to figure out where to put the deuterium for maximum

[4] Blagojevic *Advanced Medical Publishing* 1994

effects, how many atoms to be substituted, and how to target specific atoms for substitutions. Using their proprietary knowledge and techniques, Concert has developed a deuterated chemical entity (DCE) platform that allows them to identify and select the right form of deuterated molecules with *chemical and biological testing*. The group have demonstrated expertise in the design, synthesis, chemical analysis, bioanalytical assessment, preclinical evaluation and clinical development of deuterated compounds. They are also able to reproducibly manufacture deuterated compounds.

Concert's DCE platform

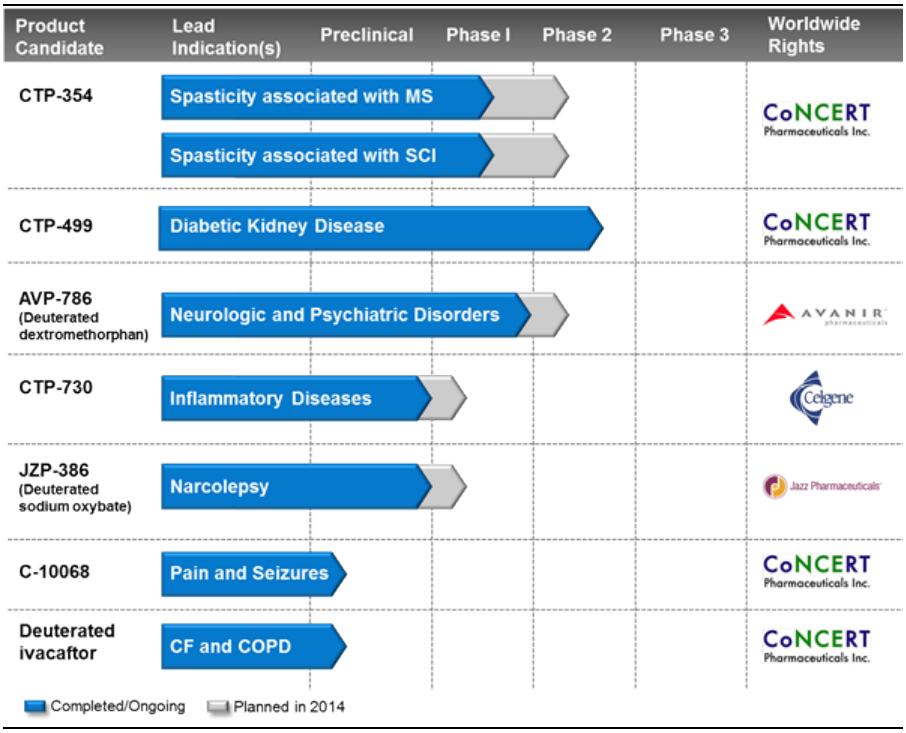
The company believes that deuterated compounds can increase the half-life in the body and increase systemic exposure, resulting in improved safety, efficacy, tolerability, and convenience. Using their proprietary knowledge and techniques, Concert strives for a development pathway that is more efficient and less expensive than the traditional development of small molecules. The company's deuterated chemical entity (DCE) platform includes (1) selecting compounds for deuteration, (2) conducting medical chemistry and chemical and biological testing of the deuterated compounds, and (3) manufacturing the deuterated compounds. Using this platform, Concert creates deuterated analogues of marketed drugs for either their approved indications or non-approved indications and analogues of previously studied compounds for which development was previously terminated.

Preliminary results supportive of the concept. An improved metabolic profile was observed in the phase-1 study of AVP-786, in which less quinidine was needed to reach desired clinical blood levels with a deuterated dextromethorphan than a non-deuterated dextromethorphan. With improved oral bioavailability, the deuterated compounds can be active at lower doses, as was seen in preclinical *in vivo studies* of CTP-354 with higher blood levels than the non-deuterated form at the same dose. An increased half-life may reduce the frequency of dosing required. In preclinical *in vivo* studies, JZP-386 showed a prolonged pharmacokinetic profile and reduced variability compared to sodium oxybate.

Concert's wholly-owned pipeline candidates

Currently, Concert has multiple product candidates in clinical development, including two wholly-owned compounds and multiple partnered candidates. Each of these candidates is being developed for oral administration.

Figure 7: Concert Pharmaceutical's product pipeline



Source: Company reports

CTP-354

CTP-354 is a subtype selective $GABA_A$ receptor modulator. '354 is a deuterated analogue of Merck's L-838417, which was found to have the therapeutic benefits of benzodiazepines without their sedative effect. Specifically, Merck's research revealed that L-838417 had 40% of the activity of benzodiazepines on the α2, α3, and α5 $GABA_A$ receptors without activity on the α1 $GABA_A$ receptor. However, L-838417 did not progress into the clinic because of limitations in bioavailability and variability. Concert designed '354 to overcome these limitations while maintaining its attractive limited sedative properties. The company believes that '354 can provide similar efficacy without the severe side effects and dosing burden by activating α2, α3, and α5 $GABA_A$ receptors without significant activation of the α1 $GABA_A$ receptor. In addition, the company believes that once-daily dosing is supported by the phase-1 data that show a long half-life in the body with low variability and high levels of $GABA_A$ receptor occupancy.

IP for '354 goes to 2029. Concert holds patents covering composition of matter of '354 and related compounds, expiring in 2029. In addition to a U.S. application claiming compositions and methods for '354, the company has issued patents in Europe and Japan that expire in 2029.

Spasticity is the initial target indication of CTP-354. '354 is being studied for spasticity in patients with multiple sclerosis and patients with spinal cord injury (SCI). Spasticity is a condition of involuntary muscle contraction, often caused by damage to the part of the brain or spinal cord that controls voluntary movement. Symptoms may range from mild tightness in the muscles to painful, uncontrollable spasms in the extremities. The American Association of Neurological Surgeons

estimates that over 12 million patients worldwide are affected by spasticity, including 80% of those with multiple sclerosis (MS). In the U.S., we believe that 136,000 of the 400,000 patients with MS are impacted by moderate to severe spasticity. In addition, although more than 80% of people with SCI have spasticity, we estimate that about 100,000 of the 270,000 patients in the U.S. with SCI experience spasticity that requires treatment. In total, we believe there are over 236,000 patients in the U.S. requiring treatment.

CTP-354 has advantages over current therapies. Current treatments for spasticity range from non-invasive to invasive procedures. The non-invasive treatments are often limited by inadequate relief of symptoms or dose-limiting side effects such as drowsiness or dizziness. The most common first-line treatments for adults in the U.S. are oral baclofen and Zanaflex (oral tizanidine). Baclofen is the most commonly prescribed treatment for spasticity, but its side effects include drowsiness, dizziness, and ataxia. Due to a short half-life, baclofen is dosed TID. If abruptly discontinued, withdrawal symptoms include hallucinations, seizures, and rebound spasticity. Zanaflex also has a short half-life, resulting in dosing every 6-8 hours up to three doses per day. In the Zanaflex clinical trials, nearly half (48%) of patients reported sedation as an adverse event. Liver function monitoring is recommended since Zanaflex can cause liver injury. In clinical studies, 5% of patients had elevated liver function tests to over three times upper limit of normal, compared to 0.4% of control patients. Less commonly used treatments of spasticity include Botox, diazepam, dantrolene, intrathecal administration of baclofen, and surgical intervention. A summary of oral antispasmodic drug therapies, with their side effects and recommended monitoring, are shown in Figure 8.

Figure 8: Side effects and monitoring required for oral antispasmodic therapies

Compound	Side effects	Monitoring
Baclofen	Sedation, excessive weakness, vertigo, mental depression, confusion, hallucinations, convulsions	Spasms, slow titration
Dantrolene sodium	Diarrhea, nausea, vomitting, weakness, hepatotoxicity	Regular liver function tests
Diazepam	Somnolence, sedation, hypotonia dependency	Spasms, sedation
Gabapentin	Somnolence, fainting, ataxia	Spasms, no abrupt withdrawal
Tizanidine	Hypotension, light-headedness, dry mouth, hepatotoxicity	Spasms, regular liver function tests

Source: Lapeyre et al, NeuroRehabilitation, 2010.; UBS research

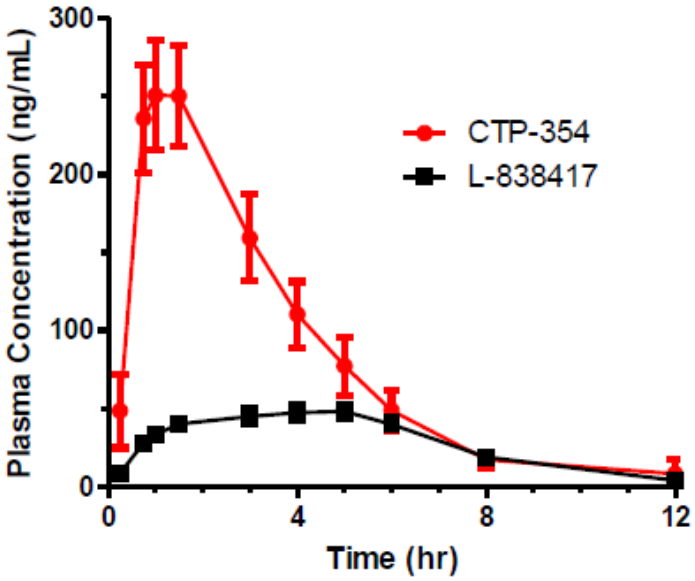
There could be broader applications of '354. Concert targets MS and SCI related spasticity as the initial indication, however, spasticity, as a chronic condition characterized by involuntary tightness, stiffness or contraction of muscles, can result from a wide range of disorders besides MS and SCI, including cerebral palsy, amyotrophic lateral sclerosis, stroke and hereditary spastic paraplegia. We can see a potential for label expansion.

Existing '354 data

The preclinical data suggests that '354 is effective without sedation. In a neuropathic pain rat model, '354 was found to be effective without sedation or ataxia. Doses between 10mg/kg and 100mg/kg were similar to that of gabapentin

dosed at 100mg/kg. 30mg/kg and 100mg/kg doses of '354 demonstrated longer duration of action than gabapentin. The minimally effective dose in the rat model of 1mg/kg provided receptor occupancy of 25% in the rat brain, while higher doses of 30mg/kg yielded receptor occupancy of 80-85%. Furthermore, PK studies in rats showed that the plasma levels of '354 were significantly higher than those of L-838417, with a maximum peak plasma concentration 4.8x higher than L-838417 and total exposure 3x higher than L-838417. A comparison of '354 and L-838417 in the rat PK study is shown in Figure 9.

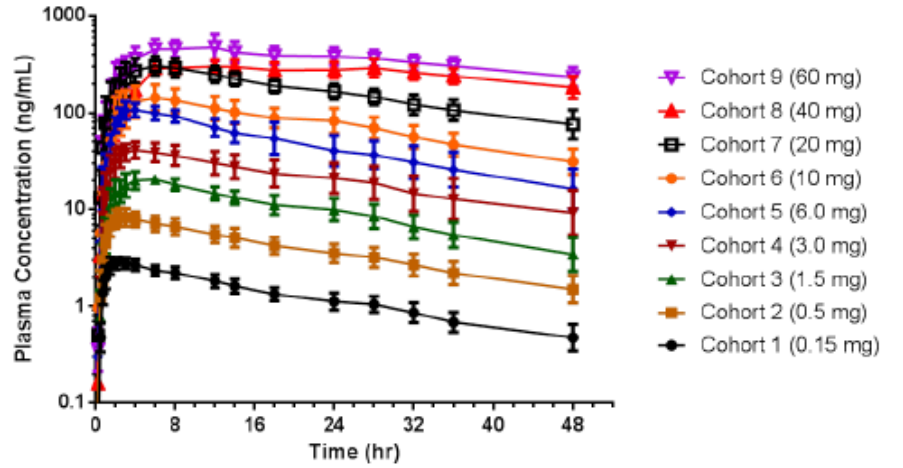
Figure 9: Oral pharmacokinetic profiles of CTP-354 and L-838417 in rats



Source: Company reports

The phase-1 single ascending dose study supports QD dosing. In August 2013, Concert completed a placebo-controlled single ascending dose study in 71 healthy adults. The volunteers were randomized 3:1 to either '354 or placebo in nine cohorts (eight with eight volunteers, one with seven volunteers), with doses ranging from 0.15mg to 60mg. Pharmacokinetic (PK) data from the study showed '354 was well-absorbed with low inter-subject variability and long plasma half-life, supporting once-daily dosing. Dosing of at least 20mg resulted in plasma concentrations over 100 ng/mL, maintained for 24 hours after dosing (see Figure 10). '354 was well-tolerated up to 60mg, but the company did not test higher doses after their phase-1 imaging study showed that high levels of $GABA_A$ receptor occupancy could be achieved with lower doses of '354. No serious adverse events were reported, and the most common adverse events included dizziness (9/54 on '354), drowsiness (7/54 on '354), prolonged QTc (4/54 on '354), and pain or muscle tightness (3/54 on '354 and 2/17 on placebo). Prolonged QTc and muscular AEs did not appear to be dose-dependent.

Figure 10: Mean plasma concentrations with '354 in single ascending dose study



Source: Company reports

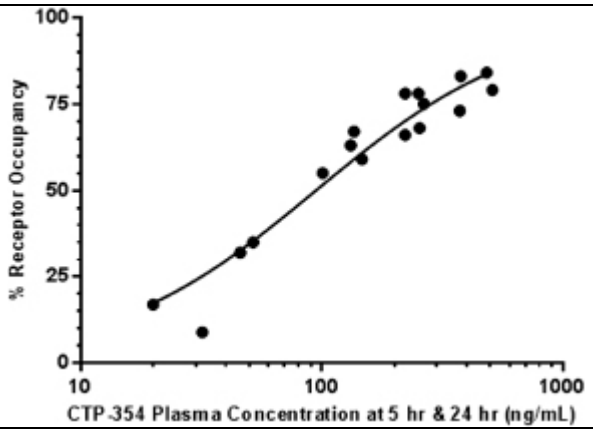
The phase-1 imaging study showed increased receptor occupancy with increasing doses up to 40mg. Currently, a phase-1 imaging study in healthy volunteers is underway using PET scanning to determine if '354 could provide higher $GABA_A$ receptor occupancy than those by benzodiazepines and to compare the relationship between '354 plasma levels and receptor occupancy. In the first part, Concert evaluated single doses of '354 in nine volunteers at doses of 4mg, 20mg, 40mg, and 60mg. Average $GABA_A$ receptor occupancy levels of 34-82% were observed five hours after the single dose. Receptor occupancy levels increased with dosing levels between 4mg and 40mg, although no significant increase was observed between 40mg and 60mg. Figure 11 shows the average GABAA receptor occupancy at five and 24 hours after dosing. A positive correlation was observed between plasma concentration and receptor occupancy (see Figure 12). Receptor occupancy levels greater than 50% was seen with plasma concentrations over 100 ng/mL. All adverse effects resolved within a day. Mild to moderate dizziness, mild drowsiness, nausea, mild euphoria, loss of balance, and lightheadedness were observed with 40mg. At the 60mg dose, adverse effects included sedation, ataxia, lightheadedness, restlessness, and irritability, and mild dizziness. In this study, 20mg did not cause sedation or ataxia while providing receptor occupancy of over 50% for 24 hours, which is significantly higher than receptor occupancies where benzodiazepines cause sedation. Concert is continuing the study to examine receptor occupancies after multiple doses of '354, from which they can select therapeutically relevant doses for phase-2 trials.

Figure 11: $GABA_A$ receptor occupancy from phase-1 imaging study

CTP-354 dose	n	Average GABAA receptor occupancy after dosing 5 hours	24 hours
4 mg	2	34%	13%
20 mg	2	63%	60%
40 mg	3	79% *	71%
60 mg	2	82%	76%

* Data from 2 of 3 volunteers. The first volunteer did not have data because of a computer error.
Source: Company reports

Figure 12: Plasma concentration and receptor occupancy from imaging study



Source: Company reports

Development path of '354

Concert signed research agreement with Fast Forward. The company signed a sponsored research agreement with Fast Forward LLC, a subsidiary of the National Multiple Sclerosis Society, in February 2012. Concert received an upfront payment of $200,000, as well as $600,000 for preclinical development milestones. Concert will make low-single digit milestone payments to Fast Forward once '354 is commercialized.

FDA Partial Clinical hold likely to be lifted with additional animal tox data. In November 2013, the FDA notified Concert of a partial clinical hold on '354, preventing single doses over 60mg per day and multiple doses over 6mg per day. The FDA, on a call with the company in December, confirmed that Concert could dose up to 6mg/day in multiple doses for 28 days. However, because a maximum tolerated dose was not determined in preclinical studies, the FDA notified Concert that they are not allowed to administer multiple doses over 6mg/day without first conducting a preclinical toxicology study. Additional studies could be conducted in one animal species to determine a maximum tolerated dose or maximum feasible dose. The company estimates that multiple doses of 6mg/day could result in receptor occupancy of 60%, which is much higher than those seen with typical clinical doses of benzodiazepines. Although Concert believes that multiple doses of 6mg/day would be sufficient to treat spasticity, they are conducting additional tox studies in 1H14 in case higher doses need to be evaluated in any of the indications. *The company does not believe that the partial clinical hold will impact timing of the phase-2. Two phase-2 studies are expected to begin in 2H14, one for*

multiple sclerosis and one for SCI, with two-way cross-over between dosing of '354 and placebo.

Phase-1 multiple ascending dose study underway with data in 2H14. Earlier this year, the company also began a multiple ascending dosing study of 2mg and 6mg doses over 10-day periods in up to 62 healthy volunteers. Concert has chosen to study lower doses than those studied in single dose, as they believe plasma concentrations will increase over the days '354 is administered daily due to its long half-life. If the partial clinical hold is lifted, the company plans to study daily doses higher than 6mg over 10-day periods.

CTP-499

CTP-499 is an analogue of the active metabolite of pentoxifylline. '499, a multi-subtype selective inhibitor of phosphodiesterases (PDEs), is a deuterated analogue of 1-(S)-5-hydroxyhexyl-3,7-dimethylxanthine (HDX). HDX is the active metabolite of pentoxifylline, which was approved in 1984 for treating symptoms of intermittent claudication from peripheral arterial disease. Initial investigator-sponsored studies of pentoxifylline suggest a reduction in albuminuria and slowing in decline of kidney function in patients with chronic kidney disease. Concert developed '499 because their preclinical research indicated that HDX may be responsible for the majority of the benefits from pentoxifylline. Currently in phase-2 studies, Concert expects to partner the phase-3 trials.

IP for '499 may go beyond 2029 with pending applications. Concert holds patents covering composition of matter of '499 and related compounds that expire in 2029. In addition to pending U.S. patent applications, the company has two applications in Europe (which would expire in 2029 and 2030) and two issued in Japan (expiring in 2029 and 2030) covering composition of matter.

T2D patients with CKD and macroalbuminuria are the targeted indications of '499

We estimate 925,000 T2D patients have CKD and macroalbuminuria. Each year, over 40,000 patients with type 2 diabetes progress to end-stage kidney failure in the U.S. '499 is being developed as an adjunct to angiotensin modulation (the current standard of care) to slow the progression of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) and macroalbuminuria. The current standard of care includes two main classes of angiotensin modulators: angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARB). Even with these treatments, however, many patients with T2D continue to experience faster-than-normal loss in renal function. We estimate that of the 23m patients with T2D in the U.S., 925,000 have CKD and macroalbuminuria.

Clinical data of '499

The phase-2 study is currently in the last of three parts. '499 is currently in phase-2 to evaluate the safety and efficacy of 600mg BID in patients with type 2 diabetic kidney disease and macroalbuminuria. All patients are also being treated with angiotensin modulators. The phase-2 study consists of three parts, and the first two parts have been completed. In Part 1, 182 patients received 600mg '499 BID for 24 weeks. Part 2, a 24-week extension study, allowed patients from Part 1

to continue receiving 600mg '499 or placebo BID. In the second part, 143 patients were enrolled, with 124 completing Part 2. Preliminary analyses have been conducted of the combined 48-week data from Parts 1 and 2. Lastly, in Part 3, patients completing Part 2 were eligible to receive 600mg '499 BID in a 48 week open-label extension. The company reported that 102 patients are enrolled in this part of the study.

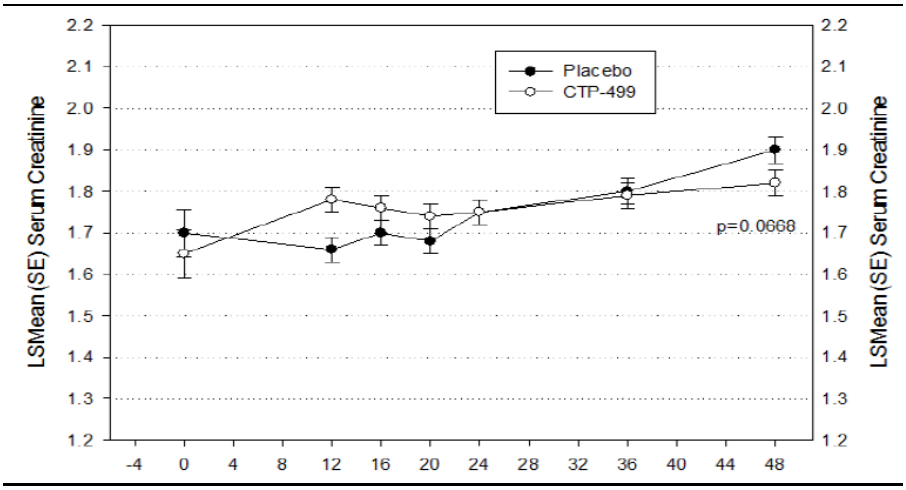
'499 appears to be safe. In terms of safety, SAEs were balanced between placebo and '499 (15.9% vs. 15.7% respectively). There were numerically more cardiac events with placebo than '499 (5.7% vs. 3.4%). Two deaths occurred in the first 24 weeks, both on '499, but neither was attributed by trial investigators to drug treatment. Discontinuations were comparable between '499 and placebo (10.1% vs. 10.2%).

The phase-2 primary endpoint at 24 weeks was not met, but preliminary analyses from 48-week data suggest a favorable trend. The primary endpoint of change in UACR (where a UACR level of over 300mg/g is considered macroalbuminuria) at 24 weeks did not reveal a meaningful difference. Subsequently, the company conducted preliminary analyses after 48 weeks which suggested a favorable trend in UACR. Specifically, the mean rise in UACR from baseline was 24 mg/g (2.2%) for '499 patients, compared to 22 mg/g (20.8%) for patients on placebo (p=0.13). Meanwhile, one of the secondary endpoints, eGFR level, showed no meaningful difference between '499 and placebo. A decline in eGFR indicates worsening of kidney function. 14% (3/58) of those on placebo experienced a 30% or greater decline in eGFR compared to 6.2% (4/65) on '499 (p=0.11). 5.2% (3/58) experienced a 40% of greater decline in eGFR compared to 1.5% (1/65) on '499 (p=0.23). It should be noted that the study was not powered for statistical significance in eGFR.

Serum creatinine may indicate slower decline in kidney function with '499. As shown in Figure 13, the mean serum creatinine level of '499 patients (n=65) increased by 0.13 mg/dL over 48 weeks, compared to 0.21 mg/dL in placebo patients (n=58). Although the difference between the two arms was not statistically significant (p=0.06), the company believes that these results suggest that the serum creatinine level of patients on '499 represents a 38% improvement from on placebo, which may indicate slower decline in kidney function with '499. In a post hoc analysis, a statistically significant effect was observed at 48 weeks in reducing the incidence of large increases in serum creatinine levels. 14% (8/58) experienced a 30% or greater increase in serum creatinine levels with '499 compared to 6% (4/65) on '499 (p=0.11; see Figure 14). 8.6% (5/58) experienced a 50% or greater increase in serum creatinine levels with '499 compared to 1.5% (1/65) on '499 (p<0.05). A 50% increase in serum creatinine levels corresponds to between 30-40% decline in eGFR. In addition, a mean rise of 2% in UACR from baseline was seen with '499, compared to 21% rise with placebo (p=0.13). The company believes the 48 week data indicates that '499 may help protect kidney function in these patients. Final top-line results for the 48 weeks of data will be reported in 1H14.

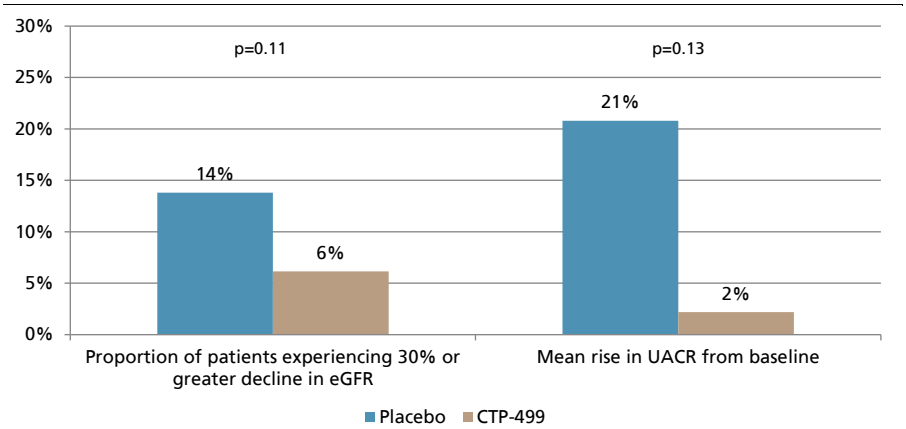
The strong trends in worsening of kidney function and albuminuria suggest CPT-499 is active, in our view.

Figure 13: CTP-499 serum creatinine levels over 48 weeks



Source: Company reports

Figure 14: Preliminary analyses based on 48 week-data for '499



Source: Company reports, UBS research

Concert's partnered programs

Since early 2012, Concert has established partnerships with Avanir, Celgene, and Jazz Pharmaceuticals. From these partnered programs, Concert is eligible for nearly $1.7b in milestones and royalties on net product sales. A summary of the partnerships is shown in Figure 15.

Figure 15: Summary of Concert's partnered programs

Company	Compound	Hydrogen analogue	Partnership Date	Potential Milestones	Terms
Avanir	AVP-786	dextromethorphan + ultra low-dose quinidine	February 2012	$166m	- $2m up front, $2m milestone payment in 2013 - Potential milestones: $4m for development, $37m for regulatory and commercial launch, $125m for sales - Potential $43m for of licensed products that do not require quinidine - Mid-single to low-double digit royalties
Celgene	CTP-730	not disclosed (we believe apremilast)	April 2013	$1.4b	- $35m up front - Potential milestones for CTP-730: $23m for development, $247.5m for regulatory, $50m for sales - Second program (if CELG exercises right): $30m and potential milestones of $23m for development and $247.5 for regulatory, and $100m for sales - Third program (if CELG exercises right): $30m and potential milestones of $23m for development and $247.5 for regulatory, and $50m for sales - Fourth program (if CELG exercises option): $10m option exercise fee and potential milestones of $23m for development and $247.5m for regulatory - Mid-single to low-double digit royalties for each program
Jazz Pharmaceuticals	JZP-386	sodium oxybate	February 2013	$113m	- $4m up front - Potential miletones: $8m for development, $35m for regulatory, $70m for sales - Mid-single to low-double digit royalties

Source: Company reports, UBS research

AVP-786 (Avanir)

AVP-786 is a deuterated dextromethorphan with low-dose quinidine. In February 2012, Concert licensed the development, manufacturing, and commercialization of deuterated dextromethorphan containing products to Avanir. Avanir is focusing initially on AVP-786, a combination of deuterated dextromethorphan and an ultra-low dose of quinidine for neurologic and psychiatric disorders. Currently, Avanir markets Nuedexta, a combination of dextromethorphan and quinidine, for treating pseudobulbar affect, a neurological condition with involuntary episodes of laughing or crying. Quinidine is required in Nuedexta to slow the rapid metabolism of dextromethorphan, resulting in improved effectiveness and lowered production of harmful metabolites in large quantities. However, lower doses of quinidine are desired as quinidine can cause heart rhythm changes.

Terms of the partnership include an upfront payment, milestones, and royalties. Concert will provide Avanir with R&D services until the first acceptance of an IND in the U.S., EU, or Japan. Avanir will fund all of Concert's R&D costs incurred under the program, although Avanir is currently conducting all R&D without Concert's services. Concert received an upfront payment of $2m and a milestone payment of $2m in 2013, and the company is eligible for up to $4m in development milestone payments, up to $37m in regulatory and commercial launch milestone payments, and up to $125m in sales-based milestone payments for licensed products that include a combination of deuterated dextromethorphan and quinidine. Concert is also eligible for up to an additional $43m in development milestones for licensed products that do not require quinidine, although Avanir is currently only developing deuterated dextromethorphan with quinidine. Royalties from net product sales range from mid-single to low-double digits.

IP for AVP-786 extend to 2030. Concert holds patents, expiring from 2028 to 2030, and a patent application covering composition of matter and methods of use of deuterated dextromethorphan for AVP-786. In addition, the company has issued patents in Europe and Japan that expire in 2028.

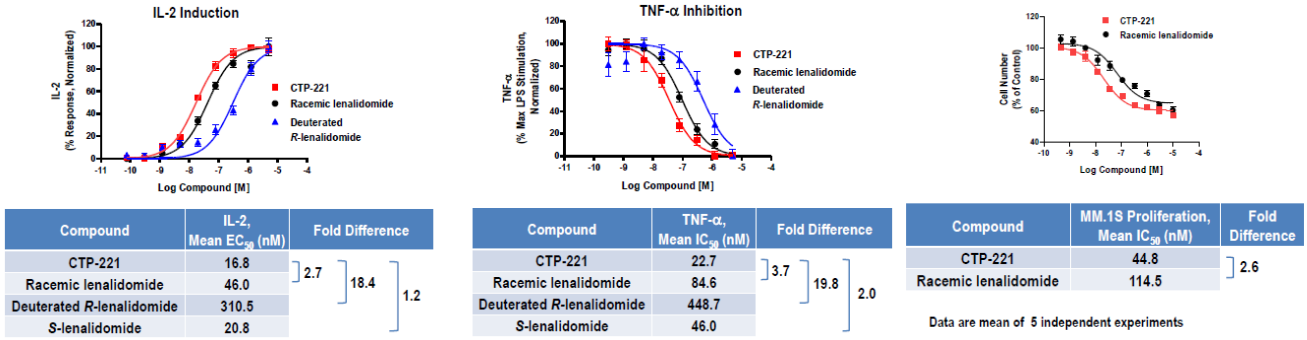
Avanir plans to advance AVP-786 into phase-2 in 2H14. In February 2013, Avanir reported positive results from a two-way crossover phase-1 study in 48 patients at a single center in Australia. AVP-786, which uses a lower dose of quinidine than AVP-923, demonstrated a similar pharmacokinetic profile to AVP-923 with comparable safety and tolerability. Avanir plans to advance AVP-786 into phase-2 and file an IND in 2H14 for treatment-resistant major depressive disorder in patients who have not responded sufficiently to conventional anti-depressants. In addition, Avanir plans to replace AVP-923 with AVP-786 in a future clinical trial. FDA agreed to an expedited development pathway allowing Avanir to reference AVP-923 data in the AVP-786 IND or future NDAs.

CTP-730 (Celgene)

CTP-730 is the first of potentially four compounds developed with Celgene. In April 2013, Concert entered into a master development and license agreement with Celgene for treating cancer or inflammation with deuterium-substituted compounds. Although the partnership includes up to four programs, with the first three non-deuterated compounds already agreed upon, Concert is initially focusing on developing CTP-730 to treat inflammatory diseases. The phase-1 study is expected to begin this year.

Deuterium substitution improves the activity of Revlimid. Concert presented a poster in 2012 which compared a deuterated S-enantiomer of Revlimid (CTP-221) to a deuterated R-enantiomer, non-deuterated S-enantiomer, and racemic Revlimid. Revlimid is dosed as a racemate due to *in vivo* interconversion of the S- and R-enantiomers. CTP-221 was found to have better pharmacological properties than Revlimid including enhanced immunomodulation (IL-2 induction, TNF-α inhibition) and anti-proliferation of cancer cells (see Figure 16). Specifically, comparing CTP-221 to racemic Revlimid, a 2.7x difference was seen in mean EC_{50} for IL-2 induction with CTP-221, a 3.7x difference was observed in mean IC_{50} for TNF-α inhibition, and a 2.6x difference was seen in mean IC_{50} for anti-proliferation. However, deuterated racemic Revlimid did not result in any advantages over Revlimid.

Figure 16: CTP-221 data showing improved pharmacological activity with deuteration



Compound	IL-2, Mean EC_{50} (nM)	Fold Difference
CTP-221	16.8	2.7
Racemic lenalidomide	46.0	18.4
Deuterated *R*-lenalidomide	310.5	1.2
S-lenalidomide	20.8	

Compound	TNF-α, Mean IC_{50} (nM)	Fold Difference
CTP-221	22.7	3.7
Racemic lenalidomide	84.6	19.8
Deuterated *R*-lenalidomide	448.7	2.0
S-lenalidomide	46.0	

Compound	MM.1S Proliferation, Mean IC_{50} (nM)	Fold Difference
CTP-221	44.8	2.6
Racemic lenalidomide	114.5	

Data are mean of 5 independent experiments

Source: Company reports

Concert may earn significant milestones and royalties in the partnership with Celgene. Concert is responsible for development costs through completion of single and multiple ascending dose phase-1 studies. For the subsequent two programs, Concert will be responsible for costs through the end of the first phase-1 trial. Concert received an upfront payment of $35m, and is eligible for up to $23m in development milestones, up to $247.5m in regulatory milestones, and up to $50m in sales-based milestones. If Celgene exercises its rights on the two additional license programs, Concert will receive $30m and be eligible for up to $23m in development milestones and up to $247.5m in regulatory milestones. For the two license programs, Concert may be eligible for up to $100m and $50m in sales-based milestones. If Celgene exercises its option on the fourth program, Concert would receive a $10m option exercise fee and could receive up to $23m in development milestones and $247.5m in regulatory milestones. For each program, Concert would receive sales royalties from mid-single digit to low double digits on net product sales.

IP related to compounds licensed to Celgene could go to 2034. Concert holds a patent and patent application covering composition of matter for deuterated analogues of the compound licensed to Celgene and applications covering other compounds licensed to the company. The patents expire in 2030 and the applications would expire between 2029 and 2034. A European patent was been issued and applications submitted in Japan for two compounds, which would expire between 2029 and 2034.

JZP-386 (Jazz Pharmaceuticals)

JZP-386 is the first analogue in a partnership with Jazz. In February 2013, Concert entered into an exclusive worldwide license agreement with Jazz Pharmaceuticals for the commercial rights to deuterated analogues of sodium oxybate, the active ingredient in Xyrem. Jazz markets Xyrem in the U.S. for treating symptoms of narcolepsy, specifically cataplexy and excessive daytime sleepiness. JZP-386, which is the first analogue of focus in the partnership, has shown a prolonged pharmacokinetic profile and reduced variability in preclinical *in vivo* studies. The phase-1 study is expected to begin, as well as yield initial data, in 2014.

Concert will conduct studies through the end of phase-1. In addition to reimbursing R&D costs, Jazz is responsible for subsequent development and commercialization of JZP-386. Concert received an upfront payment of $4 million and is eligible for up to $8m in development milestone payments, up to $35 million in regulatory milestone payments, and up to $70m in sales milestone payments. Royalties from net product sales range from mid-single to low double-digits on a country-by-country and licensed product-by-licensed product basis.

IP for deuterated sodium oxybate go to 2030 and could extend to 2032. Concert holds composition of matter patents for deuterated analogues of sodium oxybate (including JZP-386) and methods of use for treating certain diseases and disorders (including narcolepsy). Both the U.S. patent and corresponding European patent expires in 2030. The company has patent applications pending in the U.S., Europe, and Japan for JZP-386 that could go to 2032.

Management

Roger Tung, Ph.D., President and CEO. Dr. Roger Tung is the co-founder of Concert Pharmaceuticals and has served as President and CEO and a member of the company's board of directors since April 2006. Previously, he was a founding scientist at Vertex and held multiple positions at Merck, Sharp & Dohme Research Laboratories, and The Squibb Institute for Medicinal Chemistry. Dr. Tung received his B.A. in Chemistry from Reed College and his Ph.D. in Medicinal Chemistry from the University of Wisconsin-Madison.

Nancy Stuart, Chief Operating Officer. Ms. Nancy Stuart has been the Chief Operating Officer at Concert Pharmaceuticals since October 2007 and previously served as Senior Vice President, Corporate Strategy and Operations. She has held various business operations and business development positions at Amgen, Kinetix Pharmaceuticals, Vertex, and Genzyme. Ms. Stuart received her B.S. from the University of Michigan and her M.B.A. from the Simmons College Graduate School of Management.

Ryan Daws, Chief Financial Officer. Mr. Ryan Daws joined Concert Pharmaceuticals as Chief Financial Officer in January 2014. Before joining the company, he served as an independent consultant, including an engagement with Concert from September 2013 to January 2014. Previously, Mr. Daws held positions in the healthcare investment banking groups at Stifel, Nicolaus & Company and Cowen and Company. Mr. Daws received his B.S. in Finance and Organizational Management from the University of South Carolina and his International M.B.A. from University of South Carolina's Moore School of Business.

Robert Silverman, J.D., Ph.D., Senior Vice President and General Counsel. Dr. Robert Silverman has served as General Counsel of Concert Pharmaceuticals since January 2007. Previously, he held various legal roles at Millennium Pharmaceuticals, Vertex, and FMC Corporation. Dr. Silverman received his J.D. from Rutgers-Camden Law School, his Ph.D. in organic chemistry from the University of New Mexico, and his B.A. from Lehigh University.

Concert Pharmaceuticals (CNCE.O)

Income statement (US$m)	-	12/11	12/12	12/13E	% ch	12/14E	% ch	12/15E	12/16E	12/17E
Revenues	-	**19**	**13**	**32**	*149.0*	**44**	*38.4*	**55**	**82**	**105**
Gross profit	-	-	-	-	-	-	-	-	-	-
EBITDA (UBS)	-	**(10)**	**(17)**	**3**	*-*	**8**	*229.6*	**7**	**5**	**(1)**
Depreciation & amortisation	-	(2)	(1)	(1)	*-30.7*	(1)	*10.0*	(1)	(1)	(1)
EBIT (UBS)	-	**(11)**	**(19)**	**2**	*-*	**7**	*371.4*	**6**	**4**	**(3)**
Associates & investment income	-	0	0	0	-	0	-	0	0	0
Other non-operating income	-	0	0	0	-	0	-	0	0	0
Net interest	-	0	(2)	(2)	*4.8*	(2)	*0.0*	(2)	(2)	(2)
Exceptionals (incl goodwill)	-	0	0	0	-	0	-	0	0	0
Profit before tax	-	**(11)**	**(20)**	**0**	*99.1*	**6**	*-*	**4**	**2**	**(5)**
Tax	-	0	(2)	0	*89.5*	0	-	0	0	0
Profit after tax	-	**(11)**	**(22)**	**0**	*98.2*	**6**	*-*	**5**	**2**	**(5)**
Preference dividends	-	0	0	0	-	0	-	0	0	0
Minorities	-	0	0	0	-	0	-	0	0	0
Extraordinary items	-	0	0	0	-	0	-	0	0	0
Net earnings (local GAAP)	-	**(11)**	**(22)**	**0**	*98.2*	**6**	*-*	**5**	**2**	**(5)**
Net earnings (UBS)	-	**(11)**	**(22)**	**0**	*98.2*	**6**	*-*	**5**	**2**	**(5)**
Tax rate (%)	-	0.0	0.0	0.0	-	0.0	-	0.0	0.0	0.0

Per share (US$)	-	12/11	12/12	12/13E	% ch	12/14E	% ch	12/15E	12/16E	12/17E
EPS (UBS, diluted)	-	(1.56)	(2.00)	(0.04)	*98.2*	0.28	-	0.22	0.10	(0.27)
EPS (local GAAP, diluted)	-	(1.56)	(2.00)	(0.04)	*98.2*	0.28	-	0.22	0.10	(0.27)
EPS (UBS, basic)	-	(1.56)	(2.00)	(0.04)	*98.2*	0.35	-	0.27	0.12	(0.27)
Net DPS (US$)	-	0.00	0.00	0.00	-	0.00	-	0.00	0.00	0.00
Cash EPS (UBS, diluted)[1]	-	(1.34)	(1.87)	0.05	-	0.33	*511.1*	0.28	0.16	(0.18)
Book value per share	-	2.21	0.46	0.52	*13.0*	5.44	*944.1*	6.02	6.92	7.20
Average shares (diluted)	-	7.25	11.21	11.21	*0.0*	21.11	*88.3*	21.28	21.45	17.48

Balance sheet (US$m)	-	12/11	12/12	12/13E	% ch	12/14E	% ch	12/15E	12/16E	12/17E
Cash and equivalents	-	23	7	19	*148.5*	94	*403.1*	100	115	123
Other current assets	-	21	21	24	*13.7*	25	*1.4*	25	27	28
Total current assets	-	**44**	**29**	**43**	*48.7*	**118**	*175.7*	**126**	**142**	**151**
Net tangible fixed assets	-	4	3	3	*-25.0*	3	*7.7*	3	3	3
Net intangible fixed assets	-	0	0	0	-	0	-	0	0	0
Investments / other assets	-	1	1	3	*321.5*	3	*0.0*	3	3	3
Total assets	-	**49**	**33**	**49**	*47.8*	**125**	*154.3*	**132**	**148**	**158**
Trade payables & other ST liabilities	-	10	8	16	*100.4*	10	*-36.9*	11	10	14
Short term debt	-	0	0	0	-	0	-	0	0	0
Total current liabilities	-	**10**	**8**	**16**	*100.4*	**10**	*-36.9*	**11**	**10**	**14**
Long term debt	-	0	0	0	-	0	-	0	0	0
Other long term liabilities	-	14	20	27	*36.0*	22	*-18.2*	18	18	18
Preferred shares	-	0	0	0	-	0	-	0	0	0
Total liabilities (incl pref shares)	-	**25**	**28**	**43**	*54.2*	**32**	*-25.1*	**29**	**28**	**32**
Common s/h equity	-	25	5	6	*13.1*	92	*1480.2*	103	120	126
Minority interests	-	0	0	0	-	0	-	0	0	0
Total liabilities & equity	-	**49**	**33**	**49**	*47.8*	**125**	*154.3*	**132**	**148**	**158**

Cash flow (US$m)	-	12/11	12/12	12/13E	% ch	12/14E	% ch	12/15E	12/16E	12/17E
Net income (before pref divs)	-	(11)	(22)	0	*98.2*	6	-	5	2	(5)
Depreciation & amortisation	-	2	1	1	*-30.7*	1	*10.0*	1	1	1
Net change in working capital	-	(10)	(9)	17	-	(3)	-	2	5	5
Other operating	-	1	1	1	*-33.5*	1	*40.7*	1	1	1
Operating cash flow	-	**(18)**	**(28)**	**18**	*-*	**5**	*-71.5*	**9**	**10**	**3**
Tangible capital expenditure	-	0	0	0	*69.4*	0	*-40.0*	0	0	0
Intangible capital expenditure	-	0	0	0	-	0	-	0	0	0
Net (acquisitions) / disposals	-	0	0	0	-	0	-	0	0	0
Other investing	-	23	(1)	(4)	-	0	-	0	0	0
Investing cash flow	-	**23**	**(1)**	**(4)**	*-254.7*	**0**	*95.3*	**0**	**0**	**0**
Equity dividends paid	-	0	0	0	-	0	-	0	0	0
Share issues / (buybacks)	-	0	0	0	-	78	*390500.0*	0	0	0
Other financing	-	7	12	(3)	-	(5)	*-51.57*	(4)	0	0
Change in debt & pref shares	-	0	0	0	-	0	-	0	0	0
Financing cash flow	-	**7**	**12**	**(3)**	*-*	**73**	*-*	**(4)**	**0**	**0**
Cash flow inc/(dec) in cash	-	**12**	**(17)**	**11**	*-*	**78**	*619.6*	**5**	**10**	**3**
FX / non cash items	-	-	2	0	*-87.2*	(3)	-	2	5	5
Balance sheet inc/(dec) in cash	-	**-**	**(15)**	**11**	*-*	**75**	*574.6*	**7**	**15**	**8**

Source: Company accounts, UBS estimates. (UBS) metrics use reported figures which have been adjusted by UBS analysts.[1]Cash EPS (UBS, diluted) is calculated using UBS net income adding back depreciation and amortization.

Concert Pharmaceuticals (CNCE.O)

Valuation (x)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
P/E (local GAAP, diluted)	-	-	-	NM	53.4	68.3	NM	NM
P/E (UBS, diluted)	-	-	-	NM	53.4	68.3	NM	(56.0)
P/CEPS	-	-	-	NM	36.1	43.6	NM	NM
Equity FCF (UBS) yield %	-	-	-	7.1	2.0	3.5	3.7	1.2
Net dividend yield (%)	-	-	-	0.0	0.0	0.0	0.0	0.0
P/BV x	-	-	-	28.6	2.7	2.5	2.2	2.1
EV/revenues (core)	-	-	-	7.6	4.5	2.9	1.8	1.3
EV/EBITDA (core)	-	-	-	94.3	23.5	21.4	29.3	-95.3
EV/EBIT (core)	-	-	-	NM	27.1	25.6	NM	NM
EV/OpFCF (core)	-	-	-	NM	24.1	22.0	NM	NM
EV/op. invested capital	-	-	-	NM	NM	NM	NM	NM

Enterprise value (US$m)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Market cap.	-	-	-	256	256	256	256	256
Net debt (cash)	-	-	(15)	(13)	(56)	(97)	(108)	(119)
Buy out of minorities	-	0	0	0	0	0	0	0
Pension provisions/other	-	0	0	0	0	0	0	0
Total enterprise value	**-**	**-**	**-**	**243**	**200**	**159**	**149**	**137**
Non core assets	-	0	0	(1)	(1)	(1)	(1)	(1)
Core enterprise value	**-**	**-**	**-**	**242**	**199**	**158**	**147**	**136**

Growth (%)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Revenue	-	-	-34.0	149.0	38.4	24.7	48.9	27.6
EBITDA (UBS)	-	-	-76.4	-	NM	-12.7	-31.8	-
EBIT (UBS)	-	-	-64.0	-	NM	-16.1	-40.0	-
EPS (UBS, diluted)	-	-	-28.3	98.2	-	-21.8	-56.2	-
Net DPS	-	-	-	-	-	-	-	-

Margins & Profitability (%)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Gross profit margin	-	-	-	-	-	-	-	-
EBITDA margin	-	NM	NM	8.0	19.1	13.4	6.1	NM
EBIT margin	-	-58.3	-144.8	4.9	16.6	11.2	4.5	-2.8
Net earnings (UBS) margin	-	NM	NM	NM	13.3	8.4	2.5	NM
ROIC (EBIT)	-	-	>500	(19.1)	(88.0)	<-500	144.4	(115.7)
ROIC post tax	-	-	NM	NM	NM	NM	NM	NM
ROE (UBS)	-	-	(150.2)	(7.3)	12.0	4.7	1.8	(3.8)

Capital structure & Coverage (x)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Net debt / EBITDA	-	2.4	0.4	(7.3)	(11.1)	(13.6)	(22.8)	86.3
Net debt / total equity %	-	(92.8)	(145.1)	NM	(101.5)	(97.3)	(96.0)	(97.9)
Net debt / (net debt + total equity) %	-	NM	NM	NM	NM	NM	NM	NM
Net debt/EV	-	-	-	(7.7)	(47.1)	(63.5)	(78.0)	(90.5)
Capex / depreciation %	-	17.9	32.2	14.2	18.1	17.3	16.5	15.7
Capex / revenue %	-	1.5	3.6	0.4	0.5	0.4	0.3	0.2
EBIT / net interest	-	NM	NM	0.9	4.2	3.5	2.1	NM
Dividend cover (UBS)	-	-	-	-	-	-	-	-
Div. payout ratio (UBS) %	-	-	-	-	-	-	-	-

Revenues by division (US$m)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Others	-	19	13	32	44	55	82	105
Total	**-**	**19**	**13**	**32**	**44**	**55**	**82**	**105**

EBIT (UBS) by division (US$m)	-	12/11	12/12	12/13E	12/14E	12/15E	12/16E	12/17E
Others	-	(11)	(19)	2	7	6	4	(3)
Total	**-**	**(11)**	**(19)**	**2**	**7**	**6**	**4**	**(3)**

Source: Company accounts, UBS estimates. (UBS) metrics use reported figures which have been adjusted by UBS analysts.

Forecast returns

Forecast price appreciation	+68.0%
Forecast dividend yield	0.0%
Forecast stock return	+68.0%
Market return assumption	5.4%
Forecast excess return	+62.6%

Statement of Risk

We see several risks to CNCE shares, including clinical, regulatory, and commercial. Clinical risks include if CTP-354 or CTP-499 result in unforeseen safety, tolerability, or toxicity signals, or fails to yield positive clinical results. Regulatory risks include the regulatory agencies not approving the drug candidates after completing clinical trials. Commercial risks include Concert not being the only company developing deuterated analogues or compounds for the specific indications of interest, resulting in competition that may or may not materialize. In addition, generic competitors could challenge the Concert's patent estate after the company brings its products to the market.

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UBS Investment Research: Global Equity Rating Definitions

UBS 12-Month Rating	**Definition**	**Coverage**[1]	**IB Services**[2]
Buy	FSR is > 6% above the MRA.	44%	36%
Neutral	FSR is between -6% and 6% of the MRA.	45%	35%
Sell	FSR is > 6% below the MRA.	11%	23%
UBS Short-Term Rating	**Definition**	**Coverage**[3]	**IB Services**[4]
Buy	Stock price expected to rise within three months from the time the rating was assigned because of a specific catalyst or event.	less than 1%	less than 1%
Sell	Stock price expected to fall within three months from the time the rating was assigned because of a specific catalyst or event.	less than 1%	less than 1%

Source: UBS. Rating allocations are as of 31 December 2013.
1:Percentage of companies under coverage globally within the 12-month rating category. 2:Percentage of companies within the 12-month rating category for which investment banking (IB) services were provided within the past 12 months.
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UBS Securities LLC: Matthew Roden, PhD; Andrew Peters; Jeffrey Hung.

Company Disclosures

Company Name	Reuters	12-month rating	Short-term rating	Price	Price date
Concert Pharmaceuticals[2, 4, 5, 16]	CNCE.O	Not Rated	N/A	US$14.88	07 Mar 2014

Source: UBS. All prices as of local market close.
Ratings in this table are the most current published ratings prior to this report. They may be more recent than the stock pricing date

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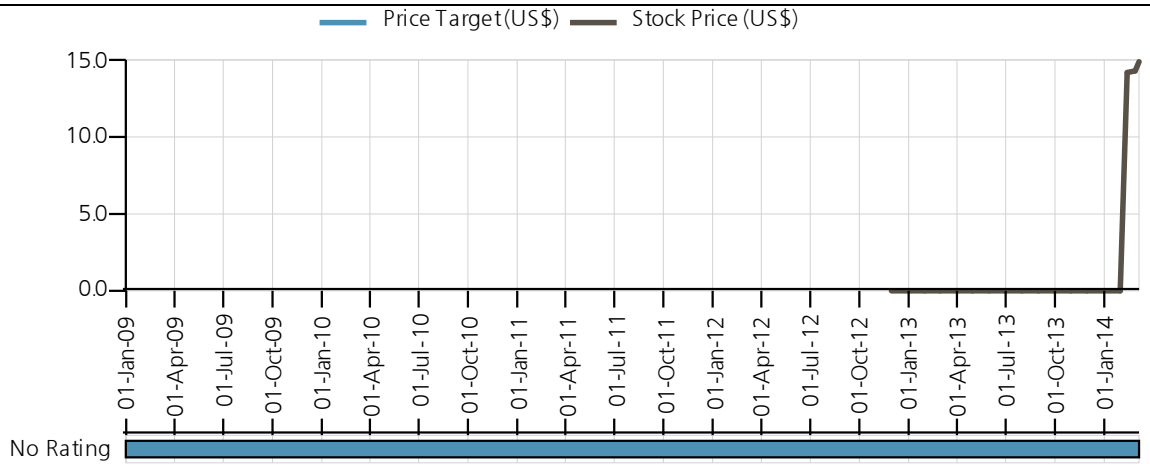
Concert Pharmaceuticals (US$)



Source: UBS; as of 07 Mar 2014

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