Trinity Delta

Serodus

3 January 2018

Entering an important year

Serodus remains on the cusp of a major inflection point, as it looks to leverage promising Phase IIa data for its lead asset, SER150 in diabetic nephropathy. The company is seeking new funds to progress its pipeline of five programmes, in addition to securing a licensing deal for SER150, an asset with blockbuster potential. Following the FDA Pre-IND meeting in September 2017, Serodus is on track to file an IND application for SER150 in H218 and expects to request Breakthrough Therapy Designation (BTD). FDA grant of BTD would clarify the regulatory pathway, shortening and facilitating SER150's route to market, and may catalyse investment and/or a partnership.

Year-end: 31 December	2013	2014	2015	2016
Sales (€m)	0.0	0.0	0.0	0.0
Adj. PBT (€m)	(1.3)	(2.0)	(3.6)	(2.7)
Net Income (€m)	(1.3)	(2.0)	(3.6)	(2.7)
Adj. EPS (€)	(0.11)	(0.09)	(0.13)	(0.06)
Cash (€m)	0.6	2.4	2.0	0.6
EBITDA (€m)	(1.3)	(2.0)	(3.6)	(2.7)

Source: Serodus accounts. Note: Adjusted numbers exclude share-based payments and exceptionals.

- **Lead candidate SER150 offers promise in diabetic nephropathy** Serodus has experienced management that has created a promising development portfolio. Lead asset, SER150, reported encouraging Phase IIa results in diabetic nephropathy in January 2017. The strength of the data has sparked interest from potential industry partners and specialist investors, and could also result in the FDA granting Breakthrough Therapy Designation.
- **Lower SER150 doses show no toxicity** SER150 was acquired from Evolva after a Phase IIa in diabetics without kidney damage showed signals of liver toxicity with a very high dose (300mg twice daily). A new Phase IIa study in diabetic nephropathy, using only 15mg and 30mg BID, showed encouraging signs of efficacy and, importantly, was well tolerated with no safety signals at all. If the positive outcomes are replicated in larger clinical trials SER150 could become a widely used add-on therapy to the current standard regimes.
- **Rest of the portfolio also shows promise** Serodus has two drugs in clinical development and three preclinical assets. Other projects are SER140, which has the potential to stop Type 2 diabetes progression; Phase I-ready SER130 for reduction of scarring in patients with myocardial infarction; SER190 for diabetic foot ulcers, and SER100, which has Orphan Drug status for PAH.
- **Additional funding required to progress SER150** Serodus delisted from the Oslo Axess Stock Exchange in February 2017 following investor feedback that its progress was not reflected in the company valuation. It is now looking to raise sufficient capital to advance its portfolio. Positively, specialist VC and pharma interest in SER150 is growing, with various ongoing discussions. Regulatory clarity during 2018 may trigger new investment and/or a deal.

Price (NOK)	Unlisted
Market Cap (NOKm)	N/A
Enterprise Value	N/A
Shares in issue	63.7m
12 month range (NOK)	N/A
Free float	N/A
Primary exchange	Unlisted
Other exchanges	N/A
Sector	Healthcare
Company Code	N/A
NOK/EUR	N/A
Corporate client	Yes

Company description:

Serodus is a private Scandinavian drug development company focused on the complications of diabetes. Its lead asset is SER150, which is in Phase II for diabetic nephropathy.

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Serodus: 2018 to be a watershed year

Serodus has built an interesting pipeline of assets targeting the complications of diabetes, through a combination of acquisition and in-licensing. Its most advanced, and commercially appealing, programme is SER150 (in-licensed from Evolva). SER150 addresses diabetic nephropathy, a large and growing clinical need, where its novel dual anti-inflammatory profile (inhibition of thromboxane synthase as well as blocking the thromboxane receptor) offers the prospect of disease modification. Extensive, and costly, clinical trials are required to assess this potential; however, the next value inflection point will arise if the FDA grants SER150 a Breakthrough Therapy Designation. Serodus is actively seeking a partner to advance SER150, in addition to external financing to progress the rest of its pipeline.

An attractive development pipeline, with an opportunity that could address diabetic nephropathy

Serodus is a Scandinavian drug development company with a strong and respected management team that has built (through acquisition and in-licensing) an attractive portfolio of pre-clinical and clinical assets. Management has a proven track record of taking products to market and executing licensing deals. The initial therapeutic focus was on cardiovascular diseases and, taking advantage of previous personal experience, the first drug that was brought in was SER100 from Zealand Pharma for pulmonary hypertension. In 2013, again exploiting previous knowledge, SER130 and SER140 were acquired through the acquisition of Phlogo, widening the focus onto diabetes and its co-morbidities. In 2014, exploiting a poorly understood set-back in a key early stage clinical trial, SER150 (previously EV-077) was in-licensed from Evolva on favourable terms.

Serodus maintains a lean structure, outsourcing required functions to an established network of specialist contract research organizations (CROs), universities, and contract manufacturers. Its strategy centres on progressing its pipeline programmes to "proof of concept" stage (typically Phase II) before either out-licensing or partnering with established larger pharmaceutical players for the later-stage, more expensive, clinical trials. The pipeline currently consists of two clinical programmes, two that could enter Phase I in the near-term (subject to securing funding), and a fifth preclinical asset. Four are being developed for diabetes-related indications; the fifth has orphan drug designation for pulmonary arterial hypertension (PAH). All address clear medical needs; however, in our view, SER150 offers most potential and is also the main focus of Serodus' R&D and business development activity.

SER150 has an attractive profile in a large market

SER150 targets a large, growing, and poorly served market segment

SER150 is an oral small molecule anti-inflammatory with a novel dual mode of action that inhibits thromboxane synthase (TS) and blocks the thromboxane receptor (TXA_2). SER150 is believed to specifically inhibit inflammatory processes in the arterioles and glomeruli of the kidney, reducing progression of renal impairment typically seen in diabetic nephropathy. Current standard of care is

ACE inhibitor or angiotensin II receptor blocker (ARB) antihypertensive therapy which, whilst effective, does not address the underlying causes of renal damage.

The pathogenesis behind progression of diabetic nephropathy is still not fully understood, with complex signalling between many classes of cells believed to result in abnormal inflammatory responses. Thromboxane is known to be an important mediator, but prior studies with a variety of blockers and antagonists failed to demonstrate significant benefit. It is thought that combined blockade of the two pathways may overcome these limitations; this underpins the rationale for examining SER150 in such nephropathies. Exhibit 1 summarises the clinical data to date for SER150.

Exhibit 1: SER150 (EV-077) clinical data disclosed to date

Stage (sponsor)	Trial details	Patient population	Results
Phase IIa (Serodus) N=72	Double-blind placebo controlled randomised 3-arm trial (placebo, 15mg and 30mg BID).	Well controlled type II diabetics with diabetic nephropathy and albuminuria.	Primary endpoint: kidney function (change in albuminuria and urinary thromboxane vs placebo after 2 and 4 weeks of treatment). Topline data confirmed strong trend towards reduced proteinuria vs placebo (statistically significant reductions in proteinuria vs baseline in both SER150 arms), with an even distribution of AEs between placebo and SER150 arms.
Phase IIa (Evolva) N=32	Double-blind placebo controlled randomised (1:1 placebo vs 300mg BID) trial.	Diabetics with no Albuminuria	Primary endpoint: platelet aggregation. Significant inhibition of platelet aggregation (arachidonic acid assay) at all time points (p=0.001). Secondary endpoints: (1) Improvements in peripheral blood flow (day 29 vs baseline, not powered for significance): macrovascular endothelial function (+43% EV-077 vs +20% placebo) and microvascular endothelial function (+108% EV-077 vs +25% placebo). (2) Reduced exercise induced proteinuria (day 29 vs baseline, not powered for significance): peak urine albuminuria level after exercise (a) all patients (-34% EV-077 vs +12% placebo) and (b) exercise completers* (-54% EV-077 vs +10% placebo). Safety data: (1) Bleeding time increase (EV-077: 4.4min at baseline to 8.6min on Day 29 vs 4.9m to 5.9min for placebo); (2) Number of serious AEs (zero in both arms); (3) patients reporting ≥ one AE (EV-077: 10 vs placebo: 6); (3) increase in liver transaminase (EV-077: 4 vs placebo: 0). Data presented at European Society of Cardiology Congress 2012.

Source: Serodus; Evolva. BID: twice daily; PK/PD: pharmacokinetic/pharmacodynamic; AE: adverse event; * In the EV-077 arm, 12 patients completed the baseline test and 10 on Day 29; and in the placebo arm, 13 completed the baseline test and 11 on Day 29.

SER150 was first evaluated in a Phase IIa trial performed by Evolva (as EV-077) in diabetic patients with no known diabetic nephropathy. This trial reported positive outcomes against both primary and secondary measures; however, signals indicative of possible liver toxicity were detected, and the programme was halted. This transient safety signal, which resolved after discontinuation, is believed to be an off-target effect connected to the 300mg twice daily dose (selected for now uncertain reasons). Serodus examined the data and an evaluation of the preclinical data package suggested that the desired efficacy could be achieved at doses an order of magnitude lower. Animal models indicate that at such doses the potential liver issues should not arise.

Phase IIa study shows positive results for both primary and secondary end-points

Top-line results from Serodus' Phase IIa study evaluating two dose strengths (15mg and 30mg twice daily) for one month in 72 patients with known diabetic nephropathy were announced in January 2017. This data showed no toxicity concerns and confirmed a strong trend towards reduced protein (albumin) excretion in the urine. No safety issues, biochemical abnormalities or bleeding tendencies were identified, with the adverse events (all mild or moderate) distributed evenly between the active and placebo groups. A statistically significant reduction in albumin excretion from baseline was observed in both the high- and low-dose groups and a very strong trend towards reduction was observed compared to placebo.

Chronic and common conditions typically require larger and costlier trial programmes

Serodus has discussed these results with a number of expert bodies; feedback supports the view that SER150 could be viewed favourably for classification as a Breakthrough Therapy by the FDA. There are multiple benefits of such a designation (summarised in Exhibit 2), including the possibility of a smaller approval study (followed by a more exhaustive Phase IV trial post marketing) and the saving of up to 3 to 4 years to the point of commercialisation.

Exhibit 2: A summary of the benefits of Breakthrough Therapy Designation

Breakthrough Therapy Designation confers many benefits, notably the time and costs savings in getting to market

Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy.

A breakthrough therapy designation conveys all of the fast track program features, more intensive FDA guidance on an efficient drug development program, an organizational commitment involving senior managers, and eligibility for rolling review and priority review. These will include:

- **holding meetings with the sponsor and the review team throughout the development of the drug;**
- **providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable;**
- **taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment;**
- **assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the cross-discipline members of the review team (ie clinical, pharmacology-toxicology, chemistry, manufacturing and control, compliance) for coordinated internal interactions and communications with the sponsor through the review division's Regulatory Health Project Manager;**
- **involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review.**

Source: FDA

IND filing and request for Breakthrough Therapy Designation expected mid-year

Serodus had a pre-IND meeting with the FDA in September 2017 to discuss the development strategy for SER150 in diabetic nephropathy. The outcome of this meeting has not been disclosed, but we understand from management that the

necessary preparatory work is ongoing to enable an IND application to be filed around H218. At which point we also expect Serodus to formally request Breakthrough Therapy Designation (BTD). The next steps in the SER150 clinical programme would depend firstly on whether BTD was granted and then on the FDA guidance given. Clarity from the FDA would also significantly de-risk SER150 from both an investor and partner perspective, potentially acting as the catalyst for new investment and/or a licensing deal.

Serodus, in our view, needs to strengthen its financial position ahead of partnering discussions

We highlight that typically, the clinical trials required for products that address such chronic and prevalent conditions tend to be both large (involving 1,000s of patients) and lengthy (usually one year plus). Therefore, we estimate that, assuming BTD was granted, the expectation would be for a Phase II/III clinical study involving 500-1,000 patients evaluated over a six month to one year period. A positive outcome would result in rapid approval conditional on corroboration of the results in a larger Phase III/IV post-marketing study that would complete within a year or so of launch. The cost of such a programme is difficult to gauge with any accuracy, but we estimate it to be c$100m to $150m. Clearly, Serodus is seeking to partner SER150 ahead of embarking on such trials. However, in our view, additional capital is needed to fund the required preparatory work, including the manufacture of sufficient active material to conclude the trials (expected to be ready H118), completion of a small pharmacology study to support the mechanism of action, and finalisation of the pre-clinical dossiers. This financing need has been partly addressed by the April 2017 NOK25m convertible loan, which provided a 12 month runway.

The diabetic nephropathy market opportunity is significant with a large and growing patient population. WHO estimates that the global number of diabetics has increased from 100m in 1980 to 442m in 2014, with adult prevalence rising from 4.7% to 8.5% in the same period. Diabetic nephropathy is one of the more important complications; whilst its understanding may have changed in recent years, it is still expected to affect around a third of diabetics. Global Data estimates that there will be c20m patients with diabetic nephropathy by 2022 in the seven major markets alone.

Even a modest success would result in a sizeable commercial opportunity

Since the inflammation is a progressive process causing loss of the renal function, SER150 could potentially become a material element of any treatment plan. Assuming the Phase IIa results are replicated in the confirmatory trials, then SER150 would likely be employed as add-on therapy to existing treatments (ACEs and ARBs). Even assuming only very modest penetration, SER150 could be a sizeable commercial success. If the profile were to show that SER150 treatment delays disease progression, or was capable of disease modification, then market potential would be significant.

More than just a one product company

Four other promising portfolio programmes

Understandably, SER150 is the primary focus; however, Serodus has four other programmes (Exhibit 3). The other diabetes-related drug candidates are SER140, which has the potential to stop progression of Type 2 diabetes; SER130, a Phase I-ready programme targeting the reduction of scarring in patients with myocardial infarction; and SER190, a novel approach to wound healing in diabetic foot ulcers. The final programme is SER100, which is ready to enter a Phase IIa trial for Pulmonary Arterial Hypertension (PAH). Next steps for these assets will be considered on a case by case basis subject to securing funding.

Exhibit 3: Details on the ex-SER150 Serodus pipeline

Product	Indication (Target)	Development stage (Next steps)	Notes
SER130	AMI in diabetics (IL-4 receptor agonist)	Pre-clinical studies completed (Phase I/IIa start)	SER130 is a peptide that activates the anti-inflammatory IL-4 receptor, which reduces the inflammatory response to an AMI (diabetics have elevated baseline levels of pro-inflammatory cytokines). By reducing inflammatory response, SER130 is expected to reduce heart scarring post-AMI.
SER140	Diabetes and co-morbidities (IL-1β receptor antagonist)	Pre-clinical studies ongoing (Phase IIa start)	Pre-clinical data in non-obese diabetic (NOD) mouse model indicate that SER140 is able to reduce the number of NOD mice that develop diabetes and preserve beta cell mass. It has no effect on HbA1c in db/db mice with a single dose. SER140 is a peptide that reduces low-grade inflammation.
SER190	Diabetic foot ulcers (IL-1β antagonist)	Exploratory stage (Preclinical package to be finalised)	Novel mechanism of action which targets the IL-1β pathway, seeking to overcome the positive feedback loop of pro-inflammatory cytokines that persists in chronic diabetic wounds.
SER100	Pulmonary arterial hypertension (ORL-1 receptor partial agonist)	Phase I completed (Phase IIa or adaptive Phase IIa/III study planned)	Phase I data (10mg BID for 2 consecutive days; n=17; placebo-controlled with crossover design) in patients with isolated systolic hypertension. Average reduction in systolic blood pressure was 7.0mm Hg (p=0.0032); and average reduction in diastolic blood pressure was 3.8mm Hg (p=0.0011). SER100 was well tolerated, with mild AEs at injection site. Granted Orphan Drug status by the FDA in October 2016.

Source: Serodus. Note: db/db mice have the leptin receptor mutated and spontaneously develop diabetes; AMI: acute myocardial infarction; AE: adverse event.

SER140 in pre-clinical testing for the prevention of diabetic progession and complications

SER140, a small (a tetramer of 14 amino acids) peptide, is a potent antagonist of the IL-1β receptor. In animal models it has been shown to protect pancreatic β-cells from cytokine-induced (L-1β mediated) apoptosis and to reduce the fundamental low-grade inflammation associated with diabetes progression. Pre-clinical studies are continuing in two animal models to establish the maximum tolerated dose. A clinical study, most likely a Phase I/IIa trial, to examine safety and tolerability in diabetic patients is planned. Successful outcomes would mean that SER140 could offer a disease modifying treatment option.

SER130 aims to reduce the scarring of cardiac infarcts in diabetics

SER130, a small (16 amino acid) peptide, is an anti-inflammatory IL-4 receptor agonist. It mimics the response of endogenous human IL-4, inhibiting a cascade of pro-inflammatory responses. It is in development as a treatment for AMI (acute myocardial infarction) scar reduction in diabetic patients. Diabetics are believed to have chronic hyperactive low-grade inflammation that exacerbates the pro-inflammatory responses seen following an AMI. SER130 would act by

restoring the balance and so, hopefully, reducing the infarct damage. The pre-clinical work is complete; SER130 is considered Phase I/IIa ready.

SER190 has a novel mechanism of action for poorly healing diabetic foot ulcers

SER190 is a small peptide IL-1 receptor antagonist which targets the IL-1β pathway. The hypothesis is that it can address persistent inflammation in poorly healing wounds, such as diabetic foot ulcers, by inhibiting the pro-inflammatory cytokine feedback loop. The SER190 preclinical data package is being finalised.

SER100 in early clinical phases for pulmonary arterial hypertension

SER100 is a small molecule targeting the ORL-1 (Opiate Receptor-Like) receptor, where its competitive activity (it is a partial agonist) is thought to result in potent but selective vasodilation. Promising pre-clinical results have shown its value in Pulmonary Arterial Hypertension and a Phase I study demonstrated good safety and tolerability. In October 2016 the FDA granted SER100 Orphan Drug status. Phase IIa trial start is subject to funding or a partnership.

Sensitivities

Serodus is exposed to all of the risks associated with a small drug development business

In common with other companies undertaking drug development, Serodus is subject to various important sensitivities. These notably include the risk of a pivotal clinical trial failing to demonstrate the expected result; the strength of the patent estate and having the ability to protect against IP litigation; the failure to obtain timely regulatory clearances; as well as the usual financing, execution, and commercial risks associated with smaller pharmaceutical companies.

Specific sensitivities include an explicit reliance on third parties to progress development, which, despite the ensuring the use of high quality CROs and third-party manufacturers, remains largely outside of their control.

Similarly, future commercial outcomes depend highly on the financial terms of potential licensing deals and collaborations, particularly for SER150.

The strength of the patent estate, and other barriers to entry, is also critical and to a degree untested. For instance, SER150 appears to have composition of matter patents lasting through to 2027. However, the degree and utility of any likely supplemental protection is as yet unknown.

Elsewhere within the portfolio, the earlier stage pipeline carries a higher risk as it still requires further clinical development and validation.

Serodus is notably dependant on a small number of experienced executives; it is their knowledge and expertise that has fashioned the compound portfolio and has driven the clinical process. The loss of such expertise would be difficult to compensate for and, in our view, would hamper continuing development.

In common with many similarly sized companies, funding remains a key sensitivity. SER150 clearly has significant potential in the treatment of diabetic nephropathy but there remain significant hurdles to overcome. Management has to seek to secure the appropriate funding and/or partnerships, on sufficiently attractive terms, to complete the next clinical phases.

Financials

Serodus requires further funding to advance SER150 and the rest of its pipeline...

Serodus' cash position at 31 March 2017 was NOK3.4m (€0.35m), down from NOK5.6m (€0.6m) at FY16. The company has a lean operating structure, with Q217 results demonstrating ongoing cost control; H117 operating spend was NOK 9.6m (€1m) 35% less than in H116. However, operating costs are likely to have increased significantly from H217 as Serodus funds the next SER150 clinical stage - including the ongoing manufacture of drug substance.

...a convertible loan provides bridge financing…

Serodus has not communicated the amounts that it needs to raise to advance its product pipeline through to value inflection point, which is understandable given the various scenarios and uncertainties. However, the priority is clearly on development of SER150 and SER140, both of which have blockbuster potential. We estimate that such a comprehensive clinical programme would cost between $100m and $150m. Ahead of securing new financing, Serodus issued a NOK24.9m convertible loan in April 2017 to existing shareholders (pro-rated to their holding) to cover base operating costs for at least the next twelve months. At end-Q217, NOK9.9m had been drawn.

…ahead of a potential financing and/or a potential licensing deal

We note that Serodus has entered into several confidentiality agreements with international pharma companies, with a view to securing a licensing deal for SER150. Deal terms are anticipated to include a significant upfront payment, with its partner bearing all subsequent costs. In our view, it would be prudent for Serodus to raise sufficient capital to complete the Phase II/III trial, assuming Breakthrough Therapy Designation is granted, (or the Phase IIb study should it be required) ahead of embarking on more serious partnering discussions to strengthen its negotiating position.

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Key personnel

Person	Position	Biography
Soren Elmann Ingerslev	Non-Executive Chairman	Elected Chairman in 2017. He is an attorney at law and partner in Elman Advokatpartnerselskab, with significant experience in company strategy and M&A. He also serves as a non-exec director on the boards of several companies.
Prof. Eva Steiness MD, DSci (Medicine)	CEO	Joined Serodus in 2010. From 1989 to 1998 she was Exec SVP for R&D at Lundbeck and was responsible for the development of Cipramil (citalopram), the blockbuster antidepressant drug. In 1998 she founded Zealand Pharma and was CEO until 2007 and led the development of lixisenatide (Lyxumia) for Type 2 diabetes (launched by Sanofi). She was also Chairman of Genmab, a Director of several Lundbeck affiliates, and Chairman of the Danish Governmental Advisory Board on Research Politics.
Dr Jurgen Langharig	SVP Business Development	Joined in 2015. Jurgen Langharig has over 30 years of experience in international marketing/business development having worked at Sandoz (now Novartis), Nycomed (now Takeda), Novo Nordisk, Zealand Pharma and most recently was VP Business Development at Bavarian Nordic.

Top 5 shareholdings

	No. of shares (m)	% holding
Viggo Harboe Holding 2006	12.6	28.3
Bjorns Invest	3.8	8.5
Danske Bank AS	3.6	8.1
Eva Steiness	2.3	5.1
MP Pensjon PK	1.8	4.0

Source: Serodus

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