Kinarus Therapeutics Holding AG

Making p38 MAP kinase inhibition viable

7 September 2022

The inhibition of the validated drug target p38 MAP kinase has been shown by many big pharmaceutical companies to result in significant anti-inflammatory activity. Unfortunately, these effects were short-lived and not a basis for a viable drug alone. That is, until the founders of Kinarus discovered and patented the use of a p38 MAP kinase in combination with another, already-approved, generic drug that does make the mechanism viable. KIN001 is that drug, with pamapimod licensed from Roche Holding AG who retain opt-in rights.

Nice idea, but pharmacodynamics was challenging… until now

Amongst the many disappointments in big pharmaceutical drug development can be the identification of a druggable target with multiple effects whose inhibition could result in the resolution of a disease, but for some reason it is let down by the pharmacodynamics (PD). PD is the study what the body does to a drug of a drug over time. Low absorption, fast excretion, or the metabolism of a drug to an inactive form can **drastically limit the potential of a new drug** that has shown good activity against a validated target in the lab. Poor PD can stop therapeutic concentrations reaching and remaining at the target and thus the drug can fail to achieve the desired effect.

The inhibition of the p38 MAP kinases in inflammatory diseases has been one of those disappointments until the founders of Swiss biotech company Kinarus discovered that a safe generic drug used in combination with the p38 MAP kinase inhibitor licensed from Roche – pamapimod – **has a viable half-life**. Step forward that combination, KIN001.

KIN001 already In Phase 2

In our valuation of Kinarus, KIN001 in neovascular, or wet age-related macular degeneration (wAMD), comprises most of the value of the company. This is despite their studies in the treatment of COVID-19 patients reading-out first because of Swiss government funding.

Kinarus's licensing strategy has resulted in them becoming a mid-stage clinical development company without the cost and time implications of drug discovery and toxicology programs. This is because Roche (Kinarus's licensor) conducted those, and other studies.

Valuation

The largest component of our valuation is a risk-adjusted NPV analysis of Kinarus's product KIN001 in wAMD, but it also includes contributions from its potential use in COVID-19 and, further out in the timeline, idiopathic pulmonary fibrosis.

Our valuation is CHF107.6m, or CHF0.10 per share.

Summary Financials

CHF '000s, y/e 31 Dec	2019A	2020A	2021A	2022E
Revenues				
EBIT	(2,267)	(1,522)	(4,720)	(7,219)
Basic EPS, (CHF)	(0.608)	(0.312)	(0.900)	(0.006)
Net Assets	2,555	1,287	(1,371)	35,997
Net Cash	1,019	319	5,225	(1,503)

Source: Company historic data, ED estimates

Company Data

EPIC	**KNRS.SW**
Share Price	CHF0.025
Market cap	CHF25m
ED Fair Value per share	CHF107.6m CHF0.10
Proforma net cash 30 Jun '22	CHF4.58m
Avg. daily volume	843,075

Share Price, CHF

Source: Google

Company Description

Kinarus is a Swiss clinical-stage biopharmaceutical company that focusses on small molecule drugs with a history of clinical use in human patients. Much of the early-stage risk is eliminated from Kinarus' projects as the dose range, mechanism of therapeutic benefit and manufacturing and regulatory considerations have already been addressed.

With the benefit of much of this work already undertaken, the cost and duration of Kinarus' clinical programs should be shorter than is the norm. Kinarus' lead drug KIN001 was originally developed by Roche for RA and after addressing its PD liability, Kinarus are developing KIN001 for the treatment of COVID-19, wAMD and IPF in Phase 2 clinical trials.

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Investment proposition

Kinarus Therapeutics Holding AG is a Swiss-listed biotechnology company that uses the industry expertise of its founders to in-license drugs that have a history of safety and some efficacy in human clinical trials, and repurpose them either by formulation or indication development to be successful drugs. Kinarus' model is to develop its drugs to clinical proof of concept, and then out-license to a partner to finish the clinical development and market the drug.

Kinarus was founded as a spin-out of Strekin AG in 2017 and recently completed a combination transaction with the public company shell Perfect Holding AG to obtain a listing on the Swiss stock market in June 2022. Now a publicly-listed entity, Kinarus' strategy remains to develop patent-protected small molecule drugs that are directed at key therapeutic targets and are already at a clinical stage. These drugs will have a documented history of safe administration to humans under the jurisdiction of a competent drug regulator and can be easily and cost-effectively manufactured.

Kinarus' first drug is the p38 MAP kinase inhibitor pamapimod which was in-licensed from Roche after the completion of two large Phase 2 studies in rheumatoid arthritis (RA). Kinarus have discovered and addressed the pharmacodynamic liability of the p38 MAP kinase inhibitor class by co-formulating pamapimod with the generic PPAR drug pioglitazone which prolongs its clinical activity beyond the two weeks usually seen with this class.

Kinarus' lead indication for KIN001 is for the treatment of wet age-related macular degeneration (wAMD) which is a large indication with the important aspect of a remaining unmet clinical need that KIN001 could address. There are a number of large potential partners for KIN001 in wAMD that include its original licensor Roche, Regeneron Pharmaceuticals and Novartis. In addition, this note includes an assessment of KIN001's prospects in the treatment of COVID-19 (which thanks to a grant from the Swiss government is already in Phase 2 and has interim results expected in Q3 2022), and idiopathic pulmonary fibrosis (IPF).

Financials

Kinarus completed a reverse takeover (RTO) transaction with the public shell company Perfect Holding SA in June 2022 by way of a share exchange. Kinarus' has reported its first half year financial results as a public company and expects to have a cash of CHF 4.48m providing a runway until at least Q1 2023. This note includes assumptions that form the basis of our financial forecasts for the year ending December 31, 2022.

Valuation

The largest component of our valuation of Kinarus is derived from a risk-adjusted NPV analysis of Kinarus's lead product KIN001 in wAMD. In addition to Kinarus' cash, we have also included contributions to our total valuation from the potential use of KIN001 in COVID-19 and, further out in the timeline, IPF.

Our fair valuation is CHF107.6m, or CHF0.10 per share.

Fixing the Achilles heel of p38 MAP kinase inhibition

Kinarus are developing an anti-inflammatory product for commercially significant indications.

One of the components of KIN001 targets the enzyme p38 mitogen-activated protein (MAP) kinase. p38 MAP kinase has long been identified as an important target in the large inflammatory indications of rheumatoid arthritis (RA), chronic airway inflammatory diseases and inflammatory bowel disease. In addition, the pandemic resulted in a number of existing anti-inflammatory drugs such as Roche's Actemra (tocilizumab) – an interleukin-6 (IL-6) receptor antagonist – that had been approved for the treatment of RA, for example, to find utility in damping down the inflammatory hyper-response in hospitalised COVID-19 patients.

Thus, had an oral p38 MAP kinase inhibitor been approved to treat RA, for example, it would have probably found utility as part of the pandemic response and would have at least been included in the randomised evaluation of COVID-19 therapy (RECOVERY) trial.

A much sought-after solution

As a highly conserved protein with a central role in the inflammatory cascade, p38 MAP kinase has long been a key target for drug developers. The isotypes of p38 MAP kinase have been identified as having a key role in regulating the biosynthesis of the proinflammatory cytokines interleukin-1β and tumour necrosis factor alpha (TNF-α), both of which are downstream of p38 MAP kinase in the inflammatory cascade. For decades TNF-α has been a viable therapeutic target of the blockbuster injectable drugs like Johnson & Johnson's **Remicade** (infliximab) and AbbVie's **Humira** (adalimumab).

At the later end of the observed inflammatory cascade, the p38 MAP kinase inhibitors have been associated with a definite effect on acute phase markers of inflammation such as C-reactive protein (CRP) after one to two weeks, but this abated in clinical studies that extended out to 12 weeks.

If the unmet need and target validation have been there to inhibit the p38 MAP kinase isotypes with an orally available small molecule, why then has a p38 MAP kinase inhibitor not so far been approved? It has not been for the lack of trying as big pharma companies such as **Novartis** with acumapimod, **GSK** with losmapimod and biotech company **Vertex** with neflamapomid have reached Phase 3 in many indications. Yet, while appearing safe and well-tolerated, these molecules have not demonstrated efficacy. Typical Phase 3 RA study designs run for at least a year in thousands of patients which is enough to demonstrate both safety and efficacy.

While p38 MAP kinase inhibition by oral drugs like Roche's pamapimod does indeed appear safe and well-tolerated, none of the 'big pharma' developers of this class of drug have yet explained why they did not demonstrate efficacy.

The inventive step of KIN001

Kinarus has answered this question.

In a study published in 2013 on Pfizer's p38 MAP kinase inhibitor PH-797804 in chronic obstructive pulmonary disease, the word tachyphylaxis was mentioned as the explanation for the highly variable clinical data. Tachyphylaxis is either the short-term response to a drug, or the onset of drug tolerance, which leads to a declining response to a drug over time. In the case of some earlier recombinant insulins in diabetic patients, the mechanism of tachyphylaxis is the induction of neutralising antibodies against the recombinant insulin.

This phenomenon has also been observed against some monoclonal antibodies that are not fully-human.

The mechanism that results in small molecule p38 MAK kinase inhibitors having a short-term effect was unknown and while it may not be archetypal tachyphylaxis, the effect – that renders an initially active drug against a validated target, inactive over time – is the same.

The founders of Kinarus have proposed that the short-term efficacy of the p38 MAP kinase inhibitors is **mechanistic in nature** – the body's response to the drug. This is illustrated by BMS-582949 which was a p38 MAP kinase inhibitor also previously in development for the treatment of RA. In a patent disclosure, it was shown that the drug could block not only the kinase activity of p38 itself, but was also resistant to the inactivation by upstream kinases that are induced by this drug class. The relevance of this feedback mechanism was validated by BMS-582949 which demonstrated prolonged efficacy in RA patients who achieved the highest exposure to the drug. BMS-582949 was however, halted due to drug absorption issues but the example serves to demonstrate that the right drug, or as in the Kinarus approach, the right drug combination, may finally overcome the Achilles heel of p38 MAP kinase inhibition.

Two common examples of addressing these PD issues are the antibiotic **Imipenem** and SARS-CoV-2 antiviral **Paxlovid**. Merck's **Primaxin** is a highly active antibiotic but as a single agent, it is excreted by the kidney far too quickly for therapeutic levels to build up in the body. The active ingredient Pfizer's Paxlovid (nirmatrelvir), is as a single agent, metabolised in the liver to have a very short and therefore, sub-therapeutic half-life. In both cases, the co-administration of another drug (or PD booster: cilastatin in Primaxin's case and ritonavir in Paxlovid's) in lower than therapeutic doses has resolved these PD liabilities and resulted in active and commercially successful drugs.

Retaining Pamapimod anti-inflammatory activity

Kinarus' KIN001 comprises twice-daily administration of 75mg of the p38 MAP kinase inhibitor pamapimod, in-licensed from Roche, co-formulated with 5mg of the generic peroxisome proliferator-activated receptor-γ (PPAR) agonist (usually used in the treatment of type 2 diabetes), pioglitazone. Pioglitazone is usually dosed at between 30mg and 45mg once daily. The short-term treatment effect of the p38 MAP kinase inhibitor class is a result of the phosphorylation of those drugs – a process that takes about three weeks from induction to inactivation – and would need a drug holiday to reverse. This is impractical for chronic therapy but the phosphorylation that affects pamapimod, amongst other molecules, is also downregulated by pioglitazone.

A similar effect on phosphorylation and the retention of pamapimod's activity has been demonstrated in animal studies by the anti-cancer drug class the c-Jun N-terminal kinase (JNK) inhibitors, but these drugs are far too toxic to be used in chronic inflammatory indications. As a PD booster for pamapimod, pioglitazone is a much better candidate since it is **cheap, generic** and **available**, and **only requires low doses** to protect pamapimod's inactivation. This also makes clinical studies much easier since the fixed dose combination guidelines for clinical studies provide an exemption for testing both agents separately if the PD booster is a lower dose of a well-characterised and approved drug.

Like cancer therapy, the treatment of inflammatory indications can be thwarted by complicated cascades where crosstalk and pathway redundancy result in a diversion around the inhibitory step and unfortunately, continued disease. Ironically, p38 MAP kinase inhibition up-regulates JNK in such a branch that could result in pamapimod's inactivation in KIN001 if it were not for the activity of pioglitazone. There has also been a relationship reported between Type II diabetes and systemic inflammation so the dual inhibition of p38 MAP kinase and the PPAR pathway may be synergistically anti-inflammatory. The validation of the PD boosting of pamapimod was indirectly confirmed by Bristol Myers Squibb's development of the p38 MAP kinase inhibitor BMS-582949 in the treatment of RA.

While the combination of pamapimod and pioglitazone in KIN001 results in the retained p38 MAP kinase activity not seen with almost all p38 MAP kinase inhibitors alone, does the combination retain its broad anti-inflammatory activity?

In transcriptome analyses of lung tissue injury induction in mice, Kinarus have demonstrated that KIN001 was synergistic (over the individual agents) in downregulating interleukin, TNF and other proinflammatory cytokine expression.

Pamapimod license terms and advantages

Kinarus exclusively licensed global rights to pamapimod from Roche for inflammatory indications and this transaction has significant advantages compared to the development of a new p38 MAP kinase inhibitor.

Roche developed pamapimod to Phase 2, including two large studies in RA and as a result of the transaction, Kinarus has access to all the regulatory dossiers, a safety database of information on patients already treated with the molecule, and has no requirement for, or the costs of, Phase 1 or preclinical toxicology studies. Furthermore, as part of the license, Kinarus has access to 500kg of GMP-grade pamapimod active pharmaceutical ingredient (API) which saves their manufacturing costs for the foreseeable future. In addition, Kinarus has access to Roche's stability data on pamapimod and has generated their own on the fixed-dose combination co-formulated product demonstrating room temperature stability out to at least one year already.

As part of this April 2016 transaction as amended in May 2020, Roche is eligible for a single digit royalty on sales of combinations of pamapimod depending on the product's performance, and development/commercial milestones of up to CHF41 M. In addition, Roche has the right of first negotiation after reviewing the data from the Phase 2 studies.

Kinarus' Intellectual Property (IP) on KIN001

Kinarus' original license of pamapimod from Roche included not just the composition of matter patent which expired in February 2022, but access to all the data that Roche generated on pamapimod. This includes the safety database. This is important since the generation of a similar safety database and its review by regulators would be expensive and take a long time to replicate.

Just as importantly, the inventive step for the use of the combination of APIs that comprises KIN001 is covered by the issued US patent No. 112851155 and is valid until at least 2037. This US patent was the priority issuance for the granted European patent No. EU3468604 B1 and world patent treaty application PCT/EP217/063714 (WO2017/211830) which include composition of matter claims on the combination of APIs in KIN001, irrespective of therapeutic indication, and are valid until 2037.

The development strategy of KIN001

Pamapimod had completed ten clinical studies at Roche including the two large Phase 2 studies in RA and is a highly potent and selective inhibitor of p38 MAP kinase alpha. Pamapimod down regulates TNFα, IL-1β and IL-6 – three proinflammatory cytokines that are validated drug targets and have traditionally been inhibited by injectable therapeutic protein drugs. Pamapimod by contrast is an orally available small molecule with a molecular weight of 406kDa and a half-life of about four hours (which is comparable to pioglitazone's half-life and supports twice-daily dosing). Conveniently, the thiazolidinedione diabetic drug pioglitazone has also been reported to inhibit the secretion of IL-1β, IL-6 and IL-8 potentially providing the combination with additional anti-inflammatory properties over the individual drugs alone.

While Kinarus's discovery could lead to the renaissance of p38 MAP kinase inhibition in combination with the thiazolidinediones, it has been patented by Kinarus with composition of matter IP valid until 2037. Two questions come to mind on its development:

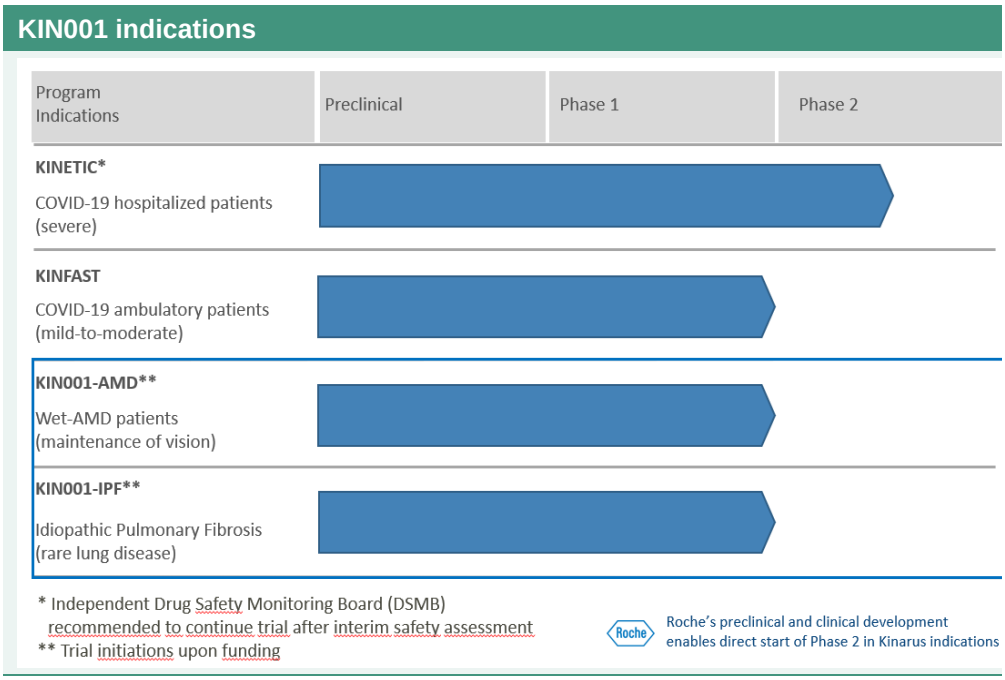
- Firstly, the bigger inflammatory indications like RA are still an unmet need, especially for an orally available and safe small molecule combination, so why is KIN001 not being developed in the large RA indication?

- Secondly, why have those pharma companies that had an active p38 MAP kinase inhibitor program not restarted them and licensed Kinarus's intellectual property?
- The first answer is due to the size of the clinical trials for a new RA drug which are likely to be in the tens of thousands of patients over at least two years (in Phase 3 alone). This is outside the funding ability of all but the biggest biotech companies.
- Secondly, just as in venture capital, it is often virtually impossible to address the 'once bitten, twice shy' dogma in pharmaceutical development or venture capital to try again with the same drug or investment class – even if a viable route for rehabilitation has been discovered. This would be until the rehabilitation was proven by later-stage clinical studies. This is now Kinarus' job.

In coming to the Kinarus story anew, we have based most of our valuation on KIN001 for the treatment of wAMD. This is partly because after the pandemic **wAMD is the much bigger indication,** although with new variant-mediated COVID-19 waves the Phase 2 studies of KIN001 – for the treatment of severe hospitalised COVID-19 patients and those ambulatory (mild-to-moderate) patients – may in time assume a greater significance.

The table below illustrates how the strategic indications for KIN001 (wAMD and IPF) fit with the opportunistic COVID-19 trials:

Kinarus' pipeline of indications for KIN001



Source: Company. Brackets define the labelled indication or use of KIN001, in strategic indications (boxed in blue) and the opportunistic COVID-19 studies which will report first

The wAMD indication is a traditional drug development path that is attractive to bigger biotech and pharma companies and KIN001 in wAMD is complementary to the existing wAMD players drugs, without the complication of emergency use authorisations and government purchasing that have characterised drugs or vaccines to treat and prevent COVID-19, respectively.

KIN001 in wet age-related macular degeneration (wAMD)

To address both the large RA study requirement and the rehabilitation of p38 MAP kinase inhibition questions, Kinarus's first Phase 2 clinical study was to have been in wAMD. wAMD is a common chronic and progressive eye disorder that causes blurred vision or a blind spot in the visual field and is caused by the abnormal growth of blood vessels that leak into the macula (part of the retina responsible for central vision). If untreated, wAMD can eventually result in blindness.

As such, this high unmet medical need has been an active area for drug developers with the early laser/photodynamic therapy era giving way to the more efficacious molecular targeting of vascular endothelial growth factor (VEGF) by the blockbuster drugs **Lucentis** (ranibizumab) and **Eylea** (afibercept). These drugs prevent the new blood vessel growth that is associated with wAMD. While effective at stabilising vision loss in most patients, anti-VEGF therapy involves an injection into the macula at the back of the eye through the front of the eye while the patient is awake. Not surprisingly, patients prefer **as few of these injections as possible** and drug company developments have largely been on extending the period between injections from what was once every six weeks with Macugen (pegaptanib sodium), to once monthly by the more efficacious Lucentis, through to bimonthly treatment after the first three months for Eylea and, most recently, once every three months after the first three months, for Beovu (brolucizumab).

These are the labelled recommendations for the induction and post-loading periods. However, such is the understandable aversion of patients to frequent intravitreal injections (IVTs), these periods tend to extend over time. In market research we have conducted with ophthalmologists, many now use a 'when required' or *pro re nata* (PRN) dosing protocol where treatment depends firstly on when the patient can bear (both emotionally and financially) to book an appointment, and secondly, the observed decline in visual acuity of the patient when they do.

Anti-VEGF mediated treatment for wAMD has probably now gone as far as it can and although other specific molecular inhibitors (such as against anti-PDGF) have been attempted in combination and failed (which required two injections at each visit) a broader anti-inflammatory approach that spares patients IVTs might be the best approach for addressing the unmet clinical need.

This is because a significant proportion of AMD heritability is associated with the genes of the immune system and especially those coding for complement components such as complement factor H which binds to CRP. In addition, the involvement of TNF-α amongst other proinflammatory cytokines in AMD has led to the conclusion that while AMD is not a classical inflammatory disease, inflammation is believed to play an indispensable role in its pathogenesis and progression.

A broad suppressor of inflammatory processes

KIN001 has many of the attributes that fit this niche in wAMD. **Not least is the fact that the combination is an oral drug which can be taken by the patient at home** saving healthcare costs and the emotional trauma of patient visits to their ophthalmologists or retinal specialists for IVTs.

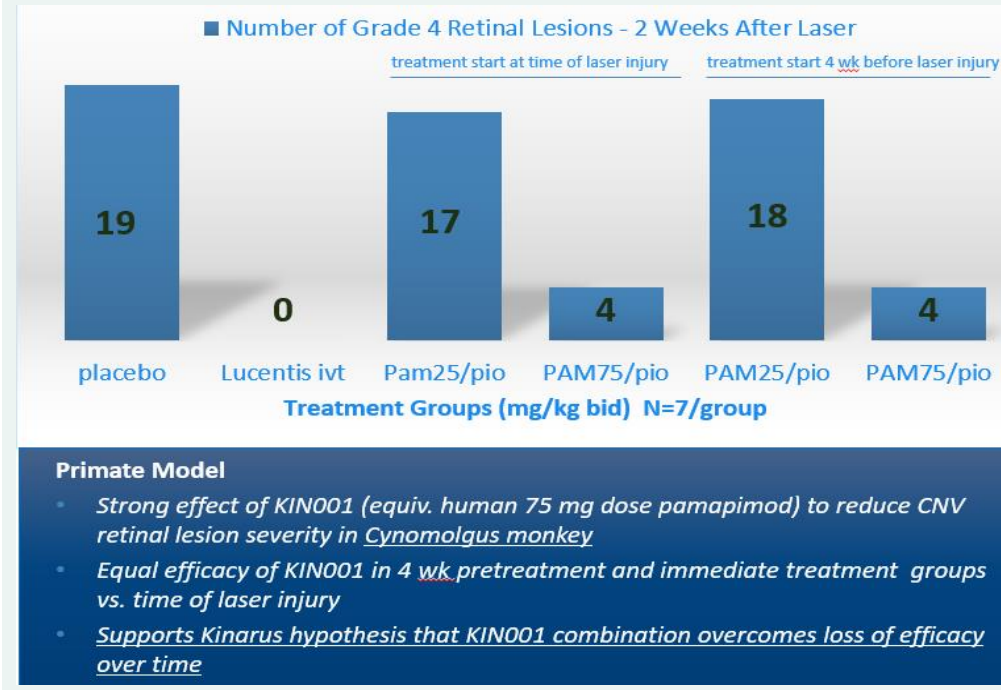
KIN001 was tested in a preclinical animal model of wAMD – the laser-induced choroidal neovascularisation (CNV) model – which has served as the backbone for testing antiangiogenic therapies.

CNV is the main pathogenic process and a leading cause of severe vision loss in wAMD and the drugs that are efficacious in the treatment of wAMD in humans show efficacy in this model. In mice, KIN001 was shown to reduce neovascularisation of laser-induced retinal lesions as well as reducing the retinal fibrotic area. In cynomolgus monkeys oral KIN001 was shown to reduce retinal lesion severity compared to placebo and to have only slightly less activity than IVT injected Lucentis.

This is an important point because an oral drug with systemic distribution should be expected to have significantly poorer activity against a drug injected directly at the disease site unless it is addressing the pathology of AMD.

Not only did oral KIN001 have **comparable activity** to IVT Lucentis, but the experiment validated p38 MAP kinase inhibition as **having utility in the treatment of wAMD**. Furthermore, KIN001 was given as a four-week pre-treatment, as well as administered at the time of the laser-induced CNV injury in monkeys (shown below). For the first time *in vivo* therefore, pamapimod (in combination with pioglitazone) demonstrated activity beyond a two-week period.

KIN001 in the CNV laser-induced model of wAMD in monkeys



Source: Company

Subject to financing availability, Kinarus are planning a 100-patient 12-month randomised placebo-controlled study of KIN001 in wAMD patients. Typically, in clinical studies with anti-VEGF agents the primary endpoint is best corrected visual acuity (BCVA, as measured by the letters the patients can read on a Snellen eye chart) in newly diagnosed patients. These are not exactly real world (RW) studies because newly diagnosed patients have a higher baseline of letters that they are able to read on the chart, so the anti-VEGF treatment of these patients typically overestimates the RW effect.

In clinical trials for wAMD, baseline BCVA is measured and treated in one eye. wAMD may not affect both patients' eyes equally at the same time but a distinct advantage for KIN001 in its proposed Phase 2 study is that any treatment effect of the oral KIN001 drug combination should be seen and measurable in both eyes (VEGF-treated and more diseased, and the less affected eye).

In Kinarus' proposed study, existing patients who are stable on their anti-VEGF IVT injections will be enrolled in a treat-and-extend-type protocol. While BVCA and safety will be secondary endpoints in the study, the primary endpoint will be the increase in treatment interval without progression (as measured by the loss of letters on the eye chart).

This study has the advantage of not changing clinical practice since apart from taking their oral drug at home (either KIN001 or placebo), the patients will attend the ophthalmologist's practice as normal and may or may not be treated with an IVT depending on the extent of their disease progression (which will be recorded as another endpoint).

We regard a significant extension of the time between injections to be of absolute importance in the commercial potential for KIN001 since it would be compatible with any IVT and offer patients (and their payers) significant benefits.

KIN001 in COVID-19

For the best possible reasons, Kinarus' clinical trial of KIN001 in wAMD has been interrupted by the pandemic due to the potential application of KIN001 in the treatment of COVID-19. During the pandemic, most pharma and biotech companies were unable to recruit their business-as-usual clinical studies because of lockdowns and the reticence of patients to attend healthcare facilities.

Drug regulators also had a role to play in this disruption by understandably prioritising clinical trials to treat or prevent (with vaccines) COVID-19 over all other studies. In addition, most governments had grant-funded programs that enabled companies to divert their applicable products into COVID-19 studies should such a rationale for their use exist.

The UK's RECOVERY study was such a program for drugs that had already been approved for other indications (such as the anti-inflammatory dexamethasone) while other branded anti-inflammatory drugs like Lilly's oral Olumiant (baricitinib) and Roche's infused Actemra – both approved for the treatment of RA – were likewise approved under emergency use authorisations (EUAs) to treat COVID-19 in hospitalised patients. One of the key discoveries from the RECOVERY trial was that dexamethasone – a generic oral glucocorticoid anti-inflammatory drug – could significantly reduce the inflammatory processes leading to the death of severe COVID-19 patients by about a third. Thus, the use of anti-inflammatory drugs in the treatment of COVID-19 was established.

As an orally active anti-inflammatory drug combination, KIN001 could find a place in the **post-pandemic era where waning vaccine immunity and new variants result in re-infections** that could emerge as waves compounding the selection of new SARS-CoV-2 variants.

Kinarus is currently conducting two Phase 2 studies partially funded by a grant from the Swiss government. The first, KINETIC study is in hospitalised patients (before the stage where Pfizer's Paxlovid was successful in high-risk and ventilated patients). The second, KINFAST study is in mild-to-moderate ambulatory COVID-19 patients (similar to Pfizer's unsuccessful intermediate-risk patient population for Paxlovid). Following the drug safety and monitoring board's (DSMB) recommendation on the study's continuation, an interim review (after the dosing of 131 patients) of the 440-patient KINETIC study in hospitalised patients and measuring the reduction in mortality amongst other endpoints, is expected in the third quarter of 2022, with completion of the study in 2023.

The KINFAST study in 400 mild-to-moderate COVID-19 patients has started at the end of August 2022 with an interim readout due in H1 2023.

The rationale for KIN001 in the treatment of symptomatic COVID-19 is not only due to the broad anti-inflammatory activity of pamapimod as boosted by pioglitazone, but the innate antiviral activity of both components. *In vitro*, a typical measure of inhibitory, or in this case antiviral activity, is the concentration of drug that results in 90% inhibition of SARS-CoV-2, or IC_{90}. For reference, two of the three FDA-approved antivirals to treat COVID-19 are Gilead Sciences' Veklury (remdesivir) and Pfizer's Paxlovid which have IC_{90}s of 2.34µM or 0.72µM, respectively, when the virus is grown in Calu-3 (lower values indicate more active inhibitors).

While the IC_{90}s of pamapimod and pioglitazone are 3.0µM and 10.0µM when tested separately, the combination is synergistic and is comparable to Veklury with the added benefit of the combination's anti-inflammatory effect. Just as it was ironic that pioglitazone has additive and separate anti-inflammatory activity in wAMD, so it can only be useful that both components have some synergistic anti-viral activity in addition to their primary anti-inflammatory activity in the treatment of moderate to severe COVID-19.

This is because if patients do not recover from initial COVID-19 and progress after about a week, or have risk factors like age or are immunocompromised, the disease can progress to its moderate stages or beyond with SpO_2 (blood oxygenation) levels below 94% and other evidence of pulmonary disease.

In many cases the sequalae, or the clinical consequences of severe cases, such as acute respiratory distress syndrome, thromboembolism, arrhythmias, and renal failure, are all mediated by inflammation and are central in the mortality associated with COVID-19.

These later stages of COVID-19 sound tailor-made for a broad anti-inflammatory like p38 MAP kinase inhibition and were justification for the non-dilutive CHF7m grant from the Swiss government to partially fund the two Phase 2 studies.

Expectations for KINETIC

While the result of the KINETIC study in hospitalised COVID-19 patients may not be the main reason to invest in Kinarus, it could provide useful indications of KIN001's activity in what we regard as the **'main event'** in Kinarus' investment proposition. **That is the activity of KIN001 in wAMD**.

The KINETIC study has already passed the first DSMB focussing on safety and the next review is in Q3 2022 where the DSMB is likely to be able to determine how many patients are required to be enrolled in KINETIC, and recommend enrolling up to that number, to obtain the best chance of demonstrating significant clinical activity. This is the strategy often taken in clinical trial designs, especially with cancer drugs.

There may be some disappointment that significant efficacy may not be demonstrated in the second DSMB review with futility, however it should be recognised that this is the most difficult to treat COVID-19 patient population and the KINETIC study is still at its early stages. The jury should remain out on KIN001 in COVID-19 until at least the results of the KINFAST study in the less severe ambulatory patients.

In our financials, we have assumed this outcome where the spend on both KINETIC and KINFAST continue into H1 2023.

Any first-time anti-inflammatory activity of KIN001 in man that is demonstrated should be regarded as a positive since many commercially viable drugs such as Viagra (sildenafil) have started off in a first, but minor indication (COVID-19 in the case of KIN001), achieving more significant commercial success in another, later indication.

KIN001 in Idiopathic pulmonary fibrosis (IPF)

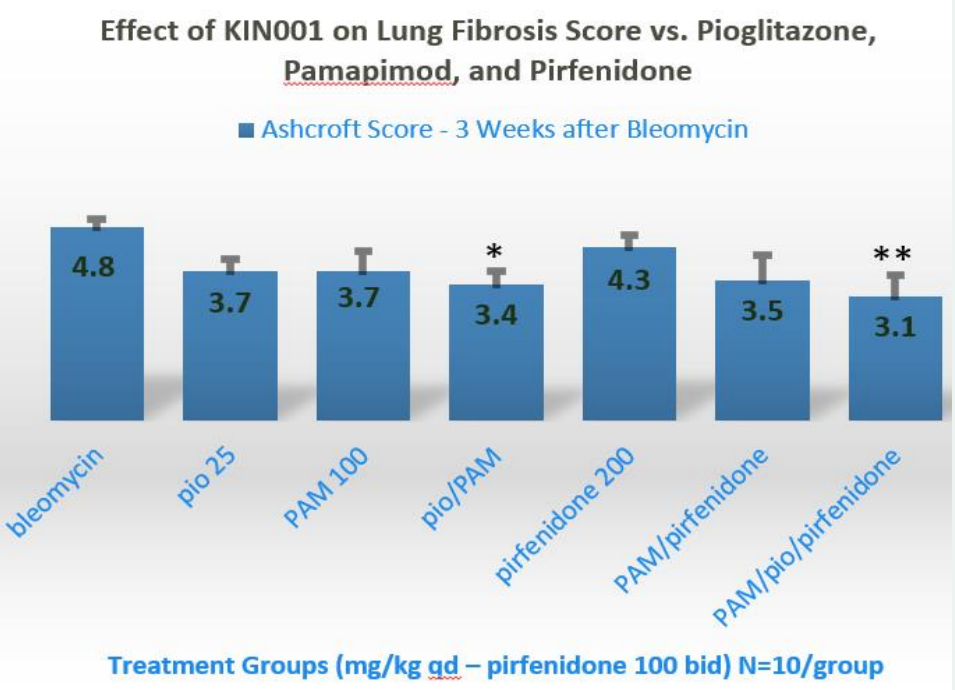
IPF is an uncommon progressive disease of the lungs without a known cause that typically occurs in patients over the age of 50. The lung tissue becomes scarred and non-functional for oxygen transfer giving rise to shortness of breath as the early sign of IPF. There are no approved drugs to modify or reverse the disease which would require airway re-modelling or reanimation of dead tissue. Instead, treatment is directed at the symptoms and includes, at its most extreme, a lung transplant and at the earlier end of the spectrum, the antioxidant N-acetylcysteine and supportive oxygen. Between those two extremes are two approved drugs – Roche's **Esbriet** (pirfenidone) and Boehringer's **Ofev** (nintedanib) – which are not disease-modifying but do help limit the symptoms of IPF.

While the aetiology or cause of IPF remains a mystery its pathology – including the influx of inflammatory cells into the lung during the acute exacerbations – has been extensively studied and concluded that inflammation is critical to the disease process. The approved drugs, and Esbriet in particular, have been described as dirty drugs because while Esbriet has a myriad of effects across the immune system, it also results in on- and off-target toxicity such as gastro-intestinal disruptions, fatigue, rash and hepatitis. The unmet need for IPF remains for an oral drug that has at least as good, or better anti-inflammatory activity than the approved drugs, but without their toxicities. Step forward KIN001.

In a preclinical mouse lung injury model of IPF **KIN001 was shown to significantly reduce lung fibrosis** alone or in combination with pirfenidone (see figure below). In biopsied samples of lung tissues from this model KIN001 also demonstrated decreased inflammatory gene expression.

Subject to funding, Kinarus are planning a 75-patient Phase 2 placebo-controlled study in IPF patients who are refractory to the standard of care and with the easily and cheaply measured forced vital capacity (FVC) as the primary endpoint. FVC is endorsed by the FDA as an outcome in IPF Phase 3 studies.

KIN001 and Lung Fibrosis Score



Source: Company

Financials

Kinarus completed a reverse takeover (RTO) transaction with the shell company Perfect Holding SA in June 2022 by way of a share exchange. Kinarus recently reported its first half-year financial results as a public company and we have used these, and some assumptions that form a basis of our financial forecasts for FY 2022. We have included the historical financials of Kinarus back to 2019 in this report.

Just before its H1 2022 report, Kinarus' recent funding history included a CHF20m convertible note facility agreement with Yorkville which is expected to start being drawn down before the end of FY 2022. In the short term, we regard this facility as enabling the preparation for Kinarus' Phase 2 study in wAMD as the key clinical trial in Kinarus' short history to date. We expect the full funding of the Phase 2 studies in wAMD and IPF to occur from either a licensing transaction, a product acquisition, or a fundraising involving either equity, debt, or a combination of all of these.

In addition, just prior to its RTO, Kinarus completed a CHF3.5m Series B private financing while in 2021, Kinarus received CHF4.4m of the CHF7.0m from the Swiss government partial funding of its COVID-19 clinical studies. Kinarus was also in receipt of a CHF3m support loan from the Canton of Basel during the pandemic years. As a result of these transactions and the RTO, Kinarus currently has 1.11bn shares in issue.

While Kinarus' Phase 2 study in hospitalised COVID-19 patients is partly grant-funded (and not a large component of our valuation), value generation from the study of KIN001 in wAMD and IPF will require **additional funding** which may, or may not be, dilutive. The former directors of Perfect Holding recognised this when they balanced Kinarus's requirement for funding with the potential upside potential of KIN001 in choosing a merger partner.

Listing

As a reverse of a private company into, effectively a public shell, and with Kinarus being a small biotech company with few full-time staff or fixed assets, Kinarus' financials are reasonably simple. With cash at the end of June 2022 of KCHF 4,583, Kinarus expects this to provide a runway until at least Q1 2023 without any additional fundraising or grant awards. With the departure of the Perfect Holding directors and subsidiaries we have assumed that G&A and R&D expenses move from KCHF1,402 and KCHF2,939 in FY 2021 to KCHF2,298 and KCHF3,027 in FY 2022, respectively.

This results in an increase in net loss from KCHF4,724 in FY 2021 to KCHF7,034 in FY 2022 although a funding transaction could result in this increasing as any cash inflows would be put in accelerating the wAMD program.

For the moment, we also carry forward Perfect Holding's KCHF478 long-term debt position that is expected to be converted into shares before the end of FY 2022. The completion of the merger also resulted in a significant increase in the resulting company's intangible assets (as a result of the recognition of Kinarus AG's investment in intellectual property and license from Roche) and will have increased Kinarus's net assets from KCHF(1,371) in FY2021 to KCHF35,997 at the end of FY 2022.

Valuation

KIN001 in wAMD

Our valuation of Kinarus is largely based on our expectations of the success of KIN001 in wAMD. To achieve this, we have assumed that Kinarus develops KIN001 until the end of Phase 2 in 2024 and then licenses the product to a bigger partner to fund the Phase 3, registration and commercialisation. In return, Kinarus receives up-front, milestone payments and royalties on KIN001 sales in wAMD at typical industry values.

To value the sales, royalties and milestones of KIN001 in wAMD, we have constructed **a wAMD model in three markets – the US, Japan and five EU countries –** based on published and commercial studies of the epidemiology of wAMD in those markets. In addition, we assume a first KIN001 launch in wAMD in the US in 2027 (and 2028 in all other markets), and loss of exclusivity (LoE) in all markets after 2037. Our estimates of wAMD patients in 2027 are 846,000, 448,000 and 1,975,000 in the US, Japan and EU, respectively. After our adjustments for the percentages of wAMD patients diagnosed, then treated and the compliance of those patients, we model uptake (or market share and launch penetration) using a Gompertz curve that typically starts at 5% in the first year and reaches 50% at peak (six years after launch).

By the last year of exclusivity, we model 256,000, 137,000 and 546,000 patients treated in the US, Japan and EU, respectively, while we estimate pricing at $10, $9 and $6 per day in those respective jurisdictions. We have assumed that, even though our model is a prevalence model, all patients we have selected will receive KIN001, even those who had been treated with anti-VEGF therapy for years and had stable visual acuity, because the additional cost will not be prohibitive and we assume that oral daily KIN001 is safe and well-tolerated.

In addition, using a reverse Gompertz curve we apply gross-to-net price discounts that start four years after launch, and continue to LoE. This results in our estimate of peak KIN001 revenues in 2032 of $1.26bn, declining to $895m in 2037. Together with the lower EU pricing and more aggressive single payer market discounts, the FY 2037 sales estimates of KIN001 in the US are $336m, while in the EU we estimate them to be $399m.

We assume that a licensing transaction is signed for KIN001 in wAMD in 2024 when a $20m upfront payment is made and additional milestones of $5m, $10m, and $20m are received on the start of Phase 3, NDA filing and FDA approval in 2025, 2026 and 2027, respectively.

We have made conservative estimates of milestone payments at global KIN001 sales hurdles ranging from $50m to $500m which, combined with the earlier upfront and milestone payments add up to $144m in total, extending out until 2029 and including pass-through milestones to Roche. We have assumed that Kinarus earns a 10% royalty on global sales, but pays Roche a single digit figure of this.

While we have discounted Kinarus' cash flows from milestones, royalties and costs for the time value of money at 12.5%, we have also risk-adjusted these cash flows at 35% – to represent the probability of success at Phase 2 – and at 70% – to represent the likelihood of a licensing transaction. While both these discounts are applied to Kinarus' royalty and milestone cash flows, we have not risk-adjusted the R&D and G&A costs that Kinarus will incur until the licensing transaction in 2024.

Our CHF68.1m valuation of KIN001 in wAMD is summarised in the table overleaf. While it is only a therapeutic analogue and was at a much later stage than where we have valued KIN001 in wAMD at, Alcon's $770m (CHF776m) recent acquisition of ophthalmic biotech company Aerie Pharmaceuticals (which had two approved drugs) indicates the value that big pharma acquires can ascribe to these businesses.

Risk-adjusted NPV valuation summary

	NPV (CHFm)	Probability of success	Probability of license	rNPV (CHFm)	rNPV (CHF/share)
KIN001 in wAMD royalties ($190m over 2027-37)	342.9	35%	70%	48.5	0.044
KIN001 in wAMD milestones between 2024 & 2029	85.2	35%	70%	17.2	0.015
Costs of development up to 2024	(3.9)	100%		(2.1)	(0.003)
Cash at 30 June 2022	4.5	100%		4.5	0.004
KIN001 in wAMD valuation	**428.8**			**68.1**	**0.061**

Source: Company data and ED estimates

KIN001 in IPF and COVID-19

The valuations of KIN001 in IPF and COVID-19 are more difficult to estimate than for the more defined and competitive wAMD market. KIN001 in the orphan indication of IPF is a specialist, but higher value per dose indication with fewer potential licensees, but is also difficult to model because the potential of KIN001 to either modify the symptoms or the disease of IPF are unknown. The $8.3bn acquisition of InterMune by Roche in 2014 is an interesting analogue but less applicable because pirfenidone had only just been approved for the treatment for IPF (and went generic in 2022). Much more applicable is the recent licensing of Redx Pharma's preclinical porcupine inhibitor RXC006 by AstraZeneca for $17m upfront and $360m in potential milestone payments. This transaction was similar to the agreement between Sanumed and United Therapeutics for the Phase 1 Wnt pathway inhibitor SM04646 for IPF in 2018 for **$10m upfront** and **up to $340m in milestones.**

To determine the present value of future transactions (where for example, the clinical development of KIN001 in IPF will start after wAMD), we use the venture capital (with double discounting) valuation methodology outlined by Harvard academic Josh Lerner. VCs use this methodology to establish a valuation for early-stage companies prior to an expected (or exit) transaction and needs only the inputs of the time in years to the transaction, its expected value and a discount rate[1]. We have used this method and with average of what Professor Lerner calls 'terminal value' – but what he means is value at an exit transaction, at a liquidation event, or even at a funding round – in this methodology.

[1] Venture Capital & Private Equity. A Casebook. Volume 2, Josh Lerner and Felda Hardymon. John Wiley & Sons, 2002, page 216.

For the two analogous IPF transactions' upfront and total milestone values discussed above, we have used the average IPF transaction values of CHF13.2m for the upfront payment and CHF343m for the for the milestones into separate Lerner's VC valuation equations. Bearing in mind that Kinarus will have to spend on the Phase 2 IPF study to get to the stage of licensing KIN001 for IPF, we have subtracted CHF8m from the upfront component before discounting.

The upfront payments in biotech transactions have a very different risk of being achieved, and over a shorter period, than the milestones. Thus, we have used a higher 15% discount rate in Lerner's VC valuation for both upfront and milestone payments, than we used for the wAMD rNPV, and have estimated the time to achieve the transactions at four years for the upfront payment, and eight years for the milestones. In addition, we have applied the additional risk-adjustments of 24.5% (the same as KIN001 in wAMD) to the upfront payment, but 80% for the milestones, **to give a present value of an IPF licensing deal at CHF19.2m**.

In the same way, a new anti-inflammatory drug to treat COVID-19 has few transaction analogues because dexamethasone was already generic or Roche's Actemra was developed in-house. There are the additional complications that COVID-19 is currently on the decline in most markets except China and the commercialisation under a EUA, or the requirement for a Phase 3 study after a successful KINETIC or KINFAST study, are unknown. On the one hand, the licensing of Lagevrio (molnupiravir) from Ridgeback Therapeutics to Merck in 2020 for the treatment of COVID-19 would be a useful analogue if the terms of the license were not so obscure.

However, Merck's FY 2021 SEC filing notes $283m in accrued royalty and milestone payments to Ridgeback so we have used a nominal $10m upfront payment and $273m in milestones as the transaction values in the same VC valuation equation as we used to estimate the value of KIN001 in IPF, above. We have subtracted a CHF5m cost from the upfront for KIN001 in COVID-19 because much of the cost has either already been spent or is grant funded.

Assuming a Phase 3 requirement, the same 15% discount rate, two and eight years until the upfront and milestone payments are received, respectively, and risk-adjustments of 25% and 80% for the upfront and milestones, **we estimate the present value of a COVID-19 licensing deal at CHF20.2m**.

Group valuation

Together, we estimate the fair value of Kinarus AG that includes its cash and KIN001 in wAMD, IPF and COVID-19 to be CHF107.6m or CHF0.10 per share.

Historic financials and forecasts

Consolidated Income Statement & Forecasts

CHF'000s, y/e 31 December	2019A	2020A	2021A	2022E
IFRS Income Statement				
Total revenue				
General & Administration expenses	(903)	(851)	(1,402)	(2,298)
R&D	(1,322)	(633)	(2,939)	(3,027)
Depreciation & amortisation	(1)	(1)	(4)	(1,520)
Reported EBIT	**(2,267)**	**(1,522)**	**(4,720)**	**(7,219)**
Reported profit before tax	**(2,280)**	**(1,522)**	**(4,724)**	**(7,034)**
Taxation				56
Basic EPS CHF	(0.6085)	(0.3117)	(0.9003)	(0.0063)
Diluted EPS CHF	(0.6085)	(0.3117)	(0.9003)	(0.0063)
Share count at end of period (basic) '000	3,747	4,883	5,247	1,113,315

Source: Company historic data, ED estimates

Consolidated Balance Sheet & Forecasts

CHF'000s, at y/e 31 March	2019A	2020A	2021A	2022E
Assets				
Non-current assets				
Tangible assets	3	2	7	9
Intangible assets	1,800	1,800	1,800	50,575
Total non-current assets	1,803	1,802	1,807	50,587
Current assets				
Trade and other receivables				
Cash and equivalents	1,019	419	5,032	1,975
Other current assets	22	49	49	174
Total current assets	1,041	468	5,352	2,149
Total assets	**2,844**	**2,270**	**7,158**	**52,736**
Equity and liabilities				
Equity				
Share capital	488	491	536	10,695
Share Premium	7,748	7,747	9,222	30,475
Retained earnings (loss)	(5,680)	(6,949)	(11,128)	(7,135)
Equity attributable to the company	2,555	1,287	(1,371)	34,034
Current liabilities				
Trade and other payables	64	100	77	342
Current provisions				1,140
Other current liabilities	226	182	1,052	869
Total current liabilities	289	983	4,129	2.351
Total non-current liabilities			4,400	14,388
Total liabilities	289	983	8,529	16,739
Total equity and liabilities	**2,844**	**2,270**	**7,158**	**52,736**

Source: Company historic, ED estimates

Consolidated Cash Flow Statements & Forecasts				
CHF'000s, y/e 31 March	**2019A**	**2020A**	**2021A**	**2022E**
Profit before taxation	(2,280)	(1,522)	(4,724)	(7,032)
Adjustment for:				
Depreciation & amortisation	1	1	4	1,520
Movements in working capital	(385)	(34)	5,245	(2,562)
Net cash generated by operating activities	(2,394)	(1,302)	(1,072)	(8,370)
Investing activities				
Capital expenditure on tangibles	(3)		(10)	
Proceeds from disposal of tangibles	(1,500)			
Acquisitions				5,483
Net cash used in investing activities	(1,503)		(10)	5,483
Financing activities				
Net proceeds from issue of shares			1,170	
Proceeds from share option exercise	10	2	4	
Transaction costs	(127)	(1)	(123)	(620)
Proceeds from subordinated loans			3,000	179
Movements in convertible debt	2,880	700	(230)	
Net cash from financing activities	2,767	701	3,821	(441)
Cash & equivalents at beginning of year	2,154	1,019	419	5,302
Cash & equivalents at end of year	**1,019**	**419**	**5,302**	**1,975**

Source: Company historic data, ED estimates.

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