Kinarus Therapeutics

Pharma and biotech

24 August 2022

A unique combination targeting unmet needs

Kinarus Therapeutics is advancing KIN001, a patented orally dosed combination of p38 mitogen-activated protein kinase (p38 MAPK) inhibitor pamapimod (in-licensed from Roche) and pioglitazone. Preclinical data suggest this combination may have antiviral, anti-inflammatory and anti-fibrotic activity. KIN001 is under development for the treatment of wet age-related macular degeneration (wet AMD), idiopathic pulmonary fibrosis (IPF) and COVID-19. Kinarus plans to start a Phase II study in wet AMD, its lead indication, before the year end, backed by preclinical data suggesting potential benefit in reducing choroidal neovascularisation (CNV) lesions. There are currently no oral drugs approved to treat wet AMD, which suggests there is a potentially significant unmet need.

KIN001 seeks to reduce wet AMD treatment burden

Wet AMD is the leading cause of vision loss in older adults in western countries, and the standard of care (SoC) requires repeated intravitreal (IVT) injections of anti-VEGF drugs, causing significant burden and compliance issues. KIN001 is designed to be complementary to anti-VEGF agents to potentially improve efficacy and reduce the frequency of required eye injections. We believe this could drive significant quality-of-life and/or compliance improvements. Capturing c 10% market share could generate sales of c $500m in the US alone.

COVID-19 and IPF may add further inflection points

Having shown in vitro antiviral activity against many COVID-19 variants, KIN001 is under evaluation in the KINETIC Phase II study in hospitalised patients (interim data expected in Q322) and is projected to start a Phase II ambulatory study shortly. The company also plans to start a Phase II study in IPF in Q123. IPF is an area of significant unmet need given high discontinuation rates with the two existing approved therapies, despite the high mortality associated with the disease.

Financials: CHF20–25m in spending before YE24

Kinarus became public in Q222 through a reverse merger transaction with Perfect Holding. Given its pro forma CHF8.8m FY21 gross cash position and assuming no change in its normalised CHF5.5m FY21 free cash flow (FCF) burn rate, these funds would be expected to last into mid-2023. The funding runway could be extended by Kinarus's recent agreement to issue up to CHF20m in convertible notes to an entity manged by Yorkville. The company expects its total expenditures to be up to CHF25m to advance all three programmes through FY24.

Historical financials

Year end	Revenue (CHFm)	PBT (CHFm)	EPS (CHF)	DPS (CHF)	P/E (x)	Yield (%)
12/20	0.0	(1.5)	(0.31)	0.00	N/A	N/A
12/21	0.0	(4.9)	(0.00)	0.00	N/A	N/A

Source: Kinarus Therapeutics. Note: 2020 accounts reflect statements of privately held Kinarus AG and 2021 statements represent pro forma financials of Kinarus Therapeutics AG following reverse merger transaction with Perfect Holding.

Price	CHF0.03
Market cap	CHF32m

Share price graph

Share details

Code	KNRS
Listing	SIX Stock Exchange
Shares in issue	1,113m
Net cash at 31 December 2021 (pro forma)	CHF5.3m

Business description

Based in Switzerland, Kinarus Therapeutics is a clinical-stage pharmaceutical company focused on advancing lead candidate KIN001 in inflammatory, fibrotic and/or viral infection related conditions. KIN001 is in Phase II studies for COVID-19, and the company plans to start Phase II studies in coming months for wet age-related macular degeneration and idiopathic pulmonary fibrosis.

Bull

- Pipeline targeting blockbuster markets.
- Human proof-of-concept for KIN001 could be shown in current and planned Phase II trials, potentially resulting in meaningful value inflection catalysts in the next 12–24 months.
- Pamapimod already has well-established safety data.

Bear

- High product concentration risk given pipeline is based on one drug candidate.
- Proof-of-concept for KIN001 not yet shown in human trials.
- Need for further funding to advance pipeline.

Analysts

Pooya Hemami OD CFA +44 (0)20 3077 5700
Soo Romanoff +44 (0)20 3077 5700
healthcare@edisongroup.com
Edison profile page

Company description

Kinarus Therapeutics (Kinarus) is a clinical-stage biopharmaceutical company, headquartered in Basel, Switzerland. It went public in June 2022 on the SIX Swiss Exchange via a reverse takeover transaction with Perfect Holding. Its lead therapeutic drug candidate, KIN001, consists of a combination of two drugs: a p38 MAPK inhibitor, pamapimod (in-licensed from Roche), and a thiazolidinedione, pioglitazone (marketed as Actos in the United States by Takeda), approved for the treatment of Type II diabetes mellitus (T2D). The company believes that this combination may have antiviral, anti-inflammatory and anti-fibrotic activity, potentially enabling an oral, effective treatment for three indications: wet AMD (also called neovascular AMD, or NVAMD), COVID-19 and IPF. The KINETIC Phase II study in hospitalised COVID-19 patients is ongoing, and the company plans to start a second study, KINFAST, in ambulatory patients in Q322. Phase II studies in wet AMD and IPF are planned in Q422 and Q123, respectively. Kinarus in August 2022 announced an agreement with an entity managed by Yorkville Advisors, whereby the company may raise up to CHF20m in convertible notes, to be drawn in tranches, over the next 36 months. We believe this facility may be used to support the funding needs for the company's planned KIN001 clinical trials in wet AMD and IPF.

We believe the company's goal is to in-license clinical-stage assets, develop proof-of-concept through its current clinical development strategy by conducting randomised fully-powered Phase II trials, and then potentially engage in value-enhancing licensing or partnership transactions. The company believes that its strategy for developing or in-licensing clinical-stage assets with existing or established safety data may result in significantly reduced development risk compared to companies advancing earlier-stage drug candidates with less safety data. Progression of the company's programmes may offer catalysts for a potential re-rating. In particular, value inflection points over the next 12 months could arise from data readouts from its Phase II COVID-19 studies.

Exhibit 1: KIN001 development plan, value inflection points and financing need

Source: Kinarus Therapeutics

Seeking to unlock p38 MAPK potential and synergies

Kinarus's lead product candidate KIN001 consists of pamapimod and pioglitazone. Pamapimod is a p38 MAP kinase inhibitor, in-licensed (with global rights) from Roche, that has been previously investigated for inflammatory conditions such as rheumatoid arthritis (RA). Alone, despite having shown adequate safety in human trials, pamapimod's treatment utility was limited given the

compensatory cellular mechanisms that lead to reduced efficacy over time. However, Kinarus believes that pioglitazone may prolong pamapimod's efficacy without compromising safety, given the company's preclinical toxicity evaluation of the combination.

Regarding efficacy, preclinical data suggest that the pamapimod/pioglitazone combination may have synergistic effects, particularly with respect to the reduction in inflammatory responses. The company is confident that its preclinical model studies across several diseases demonstrate that KIN001 has antiviral, anti-inflammatory and anti-fibrotic properties, making it potentially efficacious in all three targeted indications. KIN001 has patent protection in the United States, EU, China and other countries through to at least 2037. The product candidate's lead indication is wet AMD. The three indications pursued by Kinarus for KIN001 are described in the following sections.

KIN001 for wet AMD

Age-related macular degeneration (AMD) is the leading cause of blindness in older adults across western countries. As described in our prior sector report on AMD, there are two forms of AMD: dry and wet. Globally, the prevalence of AMD (wet and dry, all stages) in adults above age 45 is estimated at 8.7%.[1] The dry form of AMD precedes wet AMD, which accounts for 10–15% of AMD cases.

The current SoC for wet AMD is to reduce angiogenesis (blood vessel proliferation) by blocking VEGF-A binding and activity. VEGF-A is a biochemical signal protein that promotes angiogenesis and tends to be over-expressed in hypoxic environments. Currently, the only effective, reliable approved mechanism to block VEGF-A in the retina is through IVT of antibodies or antibody fragments that bind and inhibit VEGF activity. For the past decade, the two dominant anti-VEGF agents used in this indication, both delivered via IVT, have been ranibizumab (Lucentis, marketed by Roche in the United States and Novartis in ex-US markets) and aflibercept (Eylea, marketed by Regeneron and Bayer). Both products act by inhibiting VEGF-A thus blocking angiogenesis (the growth of new blood vessels) and the formation of leaky blood vessels.

Anti-VEGF-A therapies dramatically improve or stabilise vision in the large majority of wet AMD patients, and their effectiveness in wet AMD has resulted in their evaluation and approvals in other retinal conditions involving pathological angiogenesis or blood vessel leakage, such as diabetic macular edema (DME), diabetic retinopathy (DR), and macular edema following retinal vein occlusions (RVO). Hence, should KIN001 eventually gain approval in wet AMD, we anticipate that it could also be investigated for use in these eye diseases.

Under current SoC, wet AMD patients require recurring (four to eight weeks according to approved prescribing information) IVT injections of anti-VEGF-A agents to reduce areas of CNV. Eylea recorded 2021 global net sales of $9.4bn (+19% y-o-y) and Lucentis recorded CHF1.35bn (c $1.5bn) sales in 2021 in the United States (as recorded by Roche, down 6% y-o-y) and $2.16bn in ex-US markets (recorded by Novartis, up 12% y-o-y). We estimate that wet AMD represents approximately 50% of the total anti-VEGF-A retinal drug market.

We estimate that each anti-VEGF-A treatment dose (eg for Eylea and Lucentis) costs between $1,800 and $2,000 in the United States per injection, but highlight that Biogen and Samsung Bioepis recently launched Byooviz, a biosimilar to ranibizumab, and are pricing the drug 40% lower than Lucentis. Biosimilars to aflibercept are being advanced by Samsung Bioepis/Biogen (SB15), Amgen (ABP938) and Sandoz (SOK583A1).

[1] Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PT, Nemesure B, Mitchell P, Kempen J, Eye Diseases Prevalence Research Group. *Arch Ophthalmol*. 2004 Apr; 122(4):564-7

KIN001 is designed to reduce patient dependence on eye injections

VEGF-A IVT therapy requires patients (who are generally older and may have other comorbidities or mobility restrictions) to have a regular visit to their ophthalmologist to receive IVT injections. In addition to the patient discomfort and inconvenience, there may also be additional costs involved such as caregiver support, transportation, or other related needs. Further, any IVT injection carries a small but non-zero risk of endophthalmitis (intraocular inflammation), a potentially devastating condition that often leads to blindness in the affected eye. A multicentre longitudinal study involving over 88,000 injections between January 2006 and November 2016 found that the cumulative risk of developing infectious endophthalmitis after 60 IVT injections was 0.84%.[2] There is hence a need to develop new therapies to improve convenience, efficacy and/or reduce the frequency of invasive procedures. Most wet AMD patients require approximately five intraocular injections (for each affected eye) per year. Further, it has been estimated that 20–37%[3, 4] of wet AMD patients' vision continues to worsen despite anti-VEGF therapy, further prompting the need to develop new treatments.

KIN001 for wet AMD: Rationale and pre-clinical data

Oral KIN001 is designed to provide a convenient way for patients to reduce the required dosing of anti-VEGF-A injections and hence act as a complementary therapy to anti-VEGF treatments already on the market and potentially future treatments targeting this pathway. We believe that even a c 30% reduction in dosing frequency can be impactful in terms of convenience to patients and cost savings (including reduced medical visits).

Once the planned Phase II study in wet AMD commences, KIN001 would be, to our knowledge, the only oral treatment for this condition in active Phase II or proof-of-concept level studies. The drug's more convenient oral route of administration makes it generally unique among clinical-stage wet AMD drug candidates (the large majority of whom still require invasive injections and target the VEGF pathway).

KIN001 has been tested in two laser injury animal models: a mouse and primate model; both demonstrated KIN001 significantly inhibited CNV formation in the chosen models. In the mouse model, mice were divided into five treatment groups: control, pioglitazone, pamapimod, pamapimod/pioglitazone combined (KIN001) and a single IVT injection of Eylea (positive control). The KIN001 combination and individual agents (pamapimod and pioglitazone) were shown to reduce ocular CNV after laser damage. The effect on CNV is illustrated in Exhibit 2 as the area of isolectin-positive staining (marker for new blood vessels) in laser-induced CNV lesions, which shows that KIN001 reduced the isolectin-positive area to that seen with the single Eylea injection, in comparison to the control arm. Additionally, the KIN001 arm showed a lower level of fibrosis versus control (as determined through immunostaining for collagen 1a) and was generally comparable to Eylea in its effect.

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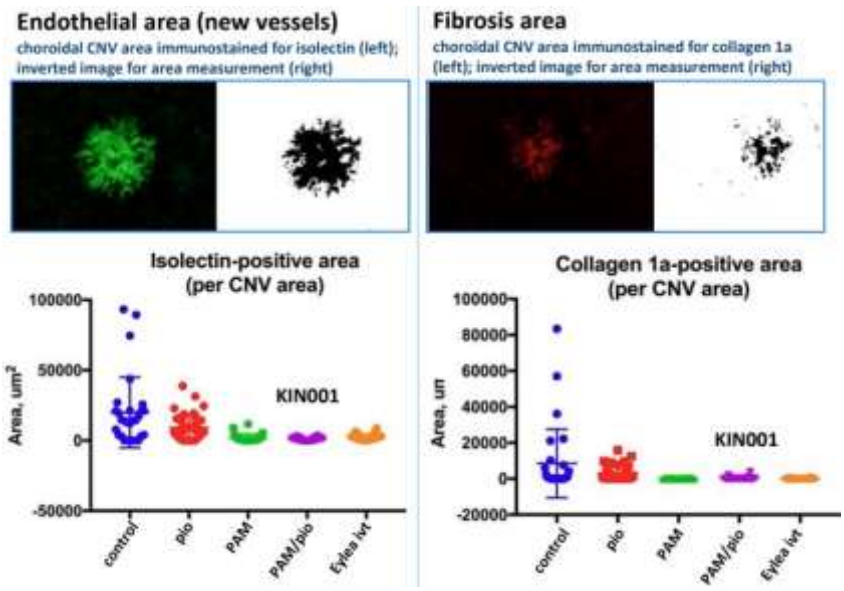
[2] Daien V, Nguyen V, Essex RW et al. *Ophthalmology*. 2018 Jan;125(1):66-74. doi: 10.1016/j.ophtha.2017.07.005. Epub 2017 Aug 8

[3] Maguire, MG et al. *Ophthalmology* 2016, 123(8), 1751 – 61

[4] Rofagha, S. et al. *Ophthalmology* 2013, 120(11):2292-9.

Exhibit 2: Mouse model showing KIN001-induced reduction of neovascularisation of laser-induced retinal lesions



Source: Kinarus Therapeutics KOL webcast presentation

KIN001 was also evaluated in a non-human primate model of laser-induced CNV (Exhibit 3), evaluating pioglitazone with either 25mg or 75mg pamapimod versus placebo, or IVT Lucentis (positive control). The number of Grade 4 retinal lesions was measured two weeks after laser injury. Results indicate a stronger effect of a fixed-dose of pioglitazone with 75mg pamapimod, which reduced the quantity of Grade 4 CNV lesions by approximately 75% versus the control group.

Exhibit 3: The effect of KIN001 on laser-induced CNV in cynomolgus monkeys (primate model)

Source: Kinarus Therapeutics KOL webcast presentation

We note that there are limitations in translating or extrapolating a laser injury model to the complex inflammatory, oxidative stress and/or metabolic factors underling AMD, as AMD is widely recognised as a multifactorial disease. Hence it is not yet known whether the results seen in preclinical data will be reproduced in human trials. But overall, the data to date support clinical evaluation of oral KIN001 as a potential complementary therapeutic for the treatment of wet AMD.

Clinical development plan for KIN001 in wet AMD

Kinarus has received regulatory approval to conduct a randomised, double-blinded 12-month Phase II study in wet AMD patients (KIN001-201). Patients with diagnosed wet AMD on stable anti-VEGF therapy will be randomised to KIN001 (oral 150mg pamapimod and 10mg pioglitazone) or

placebo. We believe most patients will be receiving either Eylea or Lucentis as their anti-VEGF therapy. The study follows a treat and extend approach to determine if KIN001 is able to prolong the treatment interval between anti-VEGF injections, by inhibiting the recurrence of macular edema, viewed as a diagnostic indicator for the recurrence of CNV. Retinal images will be captured using optical coherence tomography and evaluated centrally by an expert center for imaging in ophthalmology, which will help guide the investigator in determining the need for an anti-VEGF injection treatment. The company aims to enrol c 50 patients per arm (100 patients in total) and has powered the study to show whether KIN001 can reduce the required number of IVT injections by c 30% within the 12-month treatment period. Exploratory endpoints will include evaluation of the companion eye for conversion from the dry form of AMD to wet AMD, which may provide an initial insight as to the drug's potential effects on dry AMD. Kinarus plans to initiate the study in Q422 and potentially report top-line data in H224.

Commercial opportunity for KIN001 in wet AMD

We believe Kinarus is aiming to position KIN001 and its price so that its annual cost to the patient would be comparable to the cost savings from the reduced need for anti-VEGF-A injections and medical visits. Hence, we believe an annual price of $3,000 to $5,000 per year to be a reasonable estimate for a drug that reduces anti-VEGF-A treatments by c 30% (assuming an approximate average of five injections per year per patient). The prevalence of Caucasians in the United States with wet AMD was estimated at 1.1 million in 2015[5] and based on US National Institutes of Health (NIH) data[6] that estimates that Caucasians account for 89% of all US AMD cases, we estimate that c 1.2 million US adults have wet AMD. A 10% market share at an average yearly price of c $4,000 per year per patient could result in potential sales in the United States of $480m.

Wet AMD: Competitive landscape widening

Many companies are evaluating new therapies and modalities to extend the durability of wet AMD treatment to reduce the frequency of IVT injections.

Given that KIN001's mechanism of action is not specifically limited to the VEGF pathway, and its potential positioning as a complementary oral therapy (to Anti-VEGF), the therapy, if approved, could obtain significant commercial adoption and usage even if more potent or longer-acting anti-VEGF treatments reach the market. However, it is also possible that such longer-acting wet AMD injectable agents could restrain the commercial appeal of KIN001, as a longer interval between injection doses (if supported by clinical data), may reduce the perceived need among stakeholders for a complementary oral treatment seeking to further reduce the anti-VEGF agent injection dosing frequency.

Hence, KIN001 may face indirect competition from other emerging drugs aimed at reducing the IVT treatment burden for patients. Roche recently received two product approvals seeking to alleviate wet AMD patients. Vabysmo (faricimab), a bispecific mAB that targets and inhibits both VEGF-A and angiopoietin-2 (Ang-2, a cytokine that functions in both inflammation and angiogenesis), was approved in early 2022 with a label indicating four-month maintenance dosing and recent clinical data suggested that after two years of treatment, c 60% of patients can be treated at every four months while obtaining comparable vision gains versus aflibercept dosed every two months. Roche's Susvimo, approved in autumn 2021, is a small, refillable ocular implant designed to continuously deliver a specialised formulation of ranibizumab over time and be refilled about every six months. To maintain a competitive position, Regeneron/Bayer are assessing a higher dose

[5] Rudnicka AR, Kapetanakis VV, Jarrar Z et al. *Am J Ophthalmol*. 2015 Jul;160(1):85-93.e3. doi: 10.1016/j.ajo.2015.04.003. Epub 2015 Apr 6

[6] US National Institutes of Health. https://www.nei.nih.gov/learn-about-eye-health/eye-health-data-and-statistics

(8mg) dose of aflibercept in wet AMD in a Phase III study, dosed at every 12 or 16 weeks versus the approved dose (2mg), with results expected in H222.

There have also been relatively high-profile setbacks in the wet AMD space. Novartis's Beovu (brolucizumab), a mAB designed to reduce IVT dosing frequency versus Eylea/Lucentis, was approved in wet AMD in 2019, but has since been hampered by rare sight-threatening complications such as retinal vasculitis and intraocular inflammation, affecting market penetration (FY21 sales of $186m, notably lower than Lucentis and Eylea). AbbVie's Abicipar pegol received an FDA Complete Response letter and Kodiak's KSI-301 did not meet its Phase IIb/III primary efficacy endpoint.

Below we provide a selected list of later-stage candidates in wet AMD, which largely target VEGF. RGX-314 is worth monitoring as it is designed as a potential one-time (single-use) gene therapy product delivered via subretinal administration. RGX-314 was partnered with AbbVie in H221 and has shown a 70% reduction in the need for IVT anti-VEGF therapy post-implantation. OPT-302 is designed as an add-on to anti-VEGF-A IVT therapy. OPT-302 functions by binding and neutralising the activity of vascular endothelial growth factors C and D (VEGF-C and VEGF-D), and is intended to address the c 30% of wet AMD patients who become refractory to anti-VEGF-A therapies.

Exhibit 4: Selected list of mid- to later-stage wet AMD treatments under development

Product	Company	Stage	Mechanism	Administration	Efficacy	Notes
KSI-301	Kodiak Sciences	Phase III	Anti-VEGF antibody biopolymer conjugate. KSI-301 is intended to provide an extended ocular half-life to potentially enable longer dosing intervals.	Intravitreal injection	Did not meet primary endpoint of Phase IIb/III DAZZLE study versus aflibercept. KSI-301 was dosed every three to five months after three monthly doses.	DAYLIGHT Phase III study top-line data expected in 2023. DAYLIGHT is assessing monthly dosing.
OPT-302	Opthea	Phase III	OPT-302 is a VEGF-C/D inhibitor. Inhibition of VEGF-C/D may suppress angiogenesis. Developed as a combination therapy with SoC anti-VEGF-A therapies, as Opthea believes this achieves more complete blockage of the wet AMD mechanistic pathways.	Intravitreal injection	Phase IIb study met primary endpoint of improvement in BCVA at week 24. 2mg OPT-302 plus ranibizumab combination arm gained a mean of 14.2 letters versus 10.8 letter gain in ranibizumab alone group.	Currently two ongoing Phase III trials, ShORe and COAST, with top-line data expected near year-end 2023.
EYP-1901	EyePoint Pharmaceuticals	Phase II	Uses a bioerodible Durasert (injectable delivery system) formulation combined with vorolanib, a tyrosine kinase inhibitor with anti-VEGF effects. EYP-1901 is designed to be administered twice-yearly.	Intravitreal injection	Positive interim eight-month efficacy data from ongoing DAVIO Phase I trial. 53% of eyes did not require any supplemental anti-VEGF injections up to six months (41% up to nine months) following a single dose of EYP-1901.	Phase II trial planned in Q322. Durasert platform delivers initial burst of drug, followed by a gradual release.
RGX-314	Regenxbio	Phase II/III	One-time treatment using gene therapy using AAV capsid vector to deliver genetic cassette encoding for antibody fragment protein designed to neutralise VEGF activity. The aim is to reduce the dosage frequency of IVT anti-VEGF treatment.	Suprachoroidal injection	Positive interim data from ongoing Phase II AAVIATE trial (split into cohorts with different dose levels). RGX-314 cohorts 1–2 (n=30) six-month results showed treated patients had stable vision and retinal thickness with meaningful reduction (>70%) in treatment burden (ie frequency of anti-VEGF treatments required vs pre-RGX-314). In July 2022, enrolment was completed in cohort five of trial (total of 85 subjects dosed across five cohorts).	Partnership agreement with AbbVie announced in Q321 with $370m upfront payment to Regenxbio. Second wet AMD Phase III pivotal trial, ASCENT in collaboration with AbbVie, started in early 2022 with a BLA filing anticipated by AbbVie in 2024.
GB-102 (Sunitinib)	Graybug Vision	Phase IIb	Microparticle depot formulation of sunitinib, which is a tyrosine kinase inhibitor that blocks several receptors associated with wet AMD. The aim of GB-102 is to provide a prolonged treatment effect.	Intravitreal injection	Full Phase IIb results from ALTISSIMO (NCT03953079, where patients received drug at day 1 and month 6) showed that, of 58% of core study patients participating in a six-month extension phase (months 12–18), 55% of GB-102 1mg patients (6/11) experienced treatment duration of 12 months or longer, and these 11 patients had a 73% annualised reduction in IVT injection burden.	Graybug developed a new formulation of GB-102 intended to preserve durability and reduce microparticle dispersion. Graybug intended to start a new Phase II study using the new formulation in Q422. In June 2022, Graybug announced a review of strategic alternatives.
Lytenava (ONS-5010)	Outlook Therapeutics	Phase III	Ophthalmic formulation of bevacizumab (established anti-VEGF antibody) intended to replace off-label use of repackaged intravenous bevacizumab.	Intravitreal injection	Pivotal Phase III trial (NORSE TWO, NCT03834753) met primary endpoint, with 41.7% of subjects gaining at least 15 letters of BCVA (p=0.0052) at 12 months.	Not a direct competitor to KIN001 as its usage would be unlikely to reduce anti-VEGF dosing frequencies.

Source: Edison Investment Research, various company websites and press releases

Altogether, while the above treatment candidates may lead to reduced injectable agent treatment frequencies for wet AMD patients, we believe that, if shown to be safe and efficacious, KIN001 could still be positioned as an effective complementary therapy (to further reduce injection treatment burden) given its differentiated mechanism of action and its convenient oral administration.

Longer term, more direct competition to KIN001 could be from product candidates that similarly seek a non-invasive (topical or oral) treatment approach, possibly also intending to be used as a complementary treatment to reduce IVT treatment frequency. Among these, AKST4290 (Alkahest, subsidiary of Grifols) is an oral small-molecule CCR3 inhibitor that blocks the action of eotaxin, an immunomodulatory protein. Alkahest completed a Phase IIb study, PHTHALO-205, in H221, which evaluated the efficacy of AKST4290 versus placebo in combination with aflibercept injections in patients with newly diagnosed wet AMD.107 patients were enrolled and the primary endpoint was

mean change from baseline in Best Corrected Visual Acuity (BVCA). Results are yet to be published.

PAN-90806 (PanOptica) is a topically applied small molecule designed to block activation of VEGF receptor 2 through inhibition of the receptor's tyrosine kinase activity. In 2019, PanOptica reported positive data from its 12-week PAN-01-102 Phase I/II dose-ranging wet AMD trial (NCT03479372), which showed that 51% (26/51) of the participants completed the trial without needing any 'rescue' IVT ranibizumab treatment (at 16 weeks, or one month after treatment cessation); of these, 88% (23/26) had either clinical improvement or stability of disease. The company had been seeking potential strategic transactions to support product development. In June 2021 PanOptica entered into a licensing arrangement with Zhaoke Ophthalmology for China/South-East Asia, but limited information has been disclosed since then.

COVID-19 opportunity for KIN001

Kinarus believes that KIN001's antiviral, anti-fibrotic and anti-inflammatory properties could be valuable in the treatment of multiple stages of COVID-19. Although large-scale vaccinations and refinements in treatment algorithms, including the use of new drugs, have lessened its overall impact, COVID-19 remains a significant public health concern, particularly with the emergence of new, more transmissible variants such as Omicron BA.4 and BA.5.

The oral drugs Paxlovid (combination of protease inhibitors nirmatrelvir and ritonavir) and the RNA-dependent RNA polymerase Lagevrio (molnupiravir, Merck) have been authorised for use in high-risk COVID-19 symptomatic patients within five days of infection, but we note Paxlovid may lead to life-threatening toxicities caused by certain drug-drug interactions and both antiviral therapies may pose the threat of resistance. US officials are anticipating the possibility of another 100 million COVID-19 cases in late 2022 and given that many cases will lead to hospitalisations, potentially resulting in severe disease and/or death, there remains a significant need for additional therapies. While these drugs can be very effective when used in early stages of the disease, they are not recommended for use in patients with more severe disease, such as those who require hospitalisation. Generally speaking, antiviral or antibody drugs that target the virus itself are not expected to be efficacious once COVID-19 infection leads to more severe stages (such as those requiring hospitalisation), since at that point, treatment to modulate or control the resulting inflammatory reactions (and 'cytokine storms') would be indicated and antivirals or products targeting the virus would generally no longer be the best course on their own. KIN001's multifaceted mechanism of action, described further below, could provide therapeutic effectiveness across both the earlier and later stages of the disease.

KIN001: COVID-19 mechanism of action

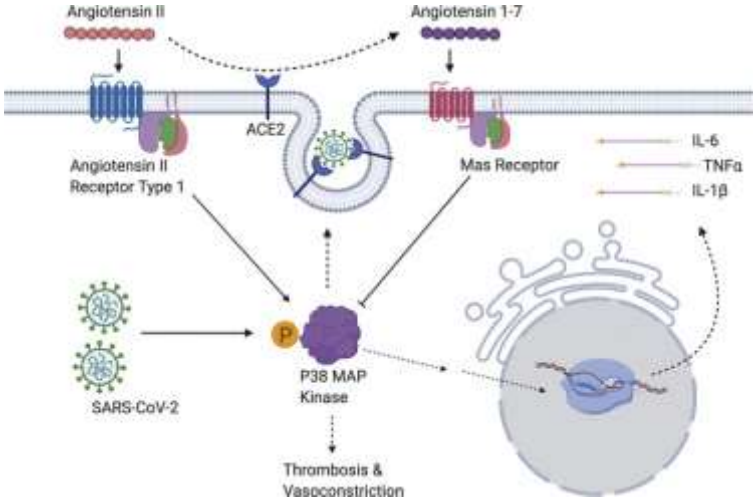
Kinarus proposes that oral KIN001 can treat COVID-19 in three ways:

1. antiviral activity, which may reduce viral load;
2. anti-inflammatory action, seeking to prevent the cytokine storm; and
3. anti-fibrotic action, aiming to prevent long-term damage to the heart, lungs and nervous system.

In particular, the KIN001 combination of pamapimod and pioglitazone is believed to have synergistic effects in treating COVID-19 patients. The p38 MAPK inhibition that occurs with pamapimod may suppress the inflammation associated with SARS-CoV-2. The inflammatory response in COVID-19 infection is what generally leads to the 'cytokine storm' associated with the condition and the resulting fibrotic damage to bodily organs including the heart, lungs and central nervous system. This inflammation may be provoked or exacerbated by disproportionately upregulated p38 activity, explained by two mechanisms:

- p38 MAPK activation promotes an inflammatory response, but in healthy cells where angiotensin-converting enzyme 2 (ACE2) is expressed (eg lungs and heart), ACE2 activity helps decrease p38 MAPK activation, thereby supressing unwanted inflammation. However, SARS-CoV-2 viral entry leads to a loss of ACE2 activity, thus leading to increased p38 MAPK activation (as reduced ACE2 activity may allow angiotensin II mediated activation of p38 to occur). p38 MAPK activation may also facilitate further viral entry.
- We also note that SARS-CoV, homologous to SARS-CoV-2, was previously shown to itself directly upregulate p38 activity.

Exhibit 5: p38 MAPK pathway with SARS-CoV-2 infection



Source: Grimes JM, Grimes KV. J Mol Cell Cardiol. 2020 Jul;144:63-65. doi: 10.1016/j.yjmcc.2020.05.007. Epub 2020 May 16. PMID: 32422320

Pioglitazone may also exhibit anti-inflammatory properties, given that it can substantially reduce pro-inflammatory cytokines such as IL-6 and TNFα in an insulin-resistant animal model.

Preclinical data show antiviral activity of KIN001

Kinarus recently conducted several in vitro studies to show the efficacy of pamapimod and pioglitazone, both separately and combined, in inhibiting SARS-CoV-2 replication in cells infected with various mutated forms of the virus, assessed using quantitative RT-PCR. The IC_{50} and IC_{90}, which are the concentrations of the drug required for 50% and 90% viral replication inhibition, respectively, were used to assess the results. Data showed that pamapimod inhibited the replication of SARS-CoV-2 with IC90 values of approximately 3 µM. Pamapimod demonstrated similar antiviral activity against the SARS-CoV-2 Wuhan type and all VoCs across several cell lines. Pioglitazone also strongly reduced SARS-CoV-2 replication, with an IC90 of c 10–15 µM.

Exhibit 6 shows the IC_{90} values of pamapimod and pioglitazone individually against SARS-CoV-2 Wuhan type and other variants of concern (VOCs) in Calu-3 cells (human lung cells that express ACE2 and Transmembrane Serine Protease 2, or TMPRSS2, endogenously).

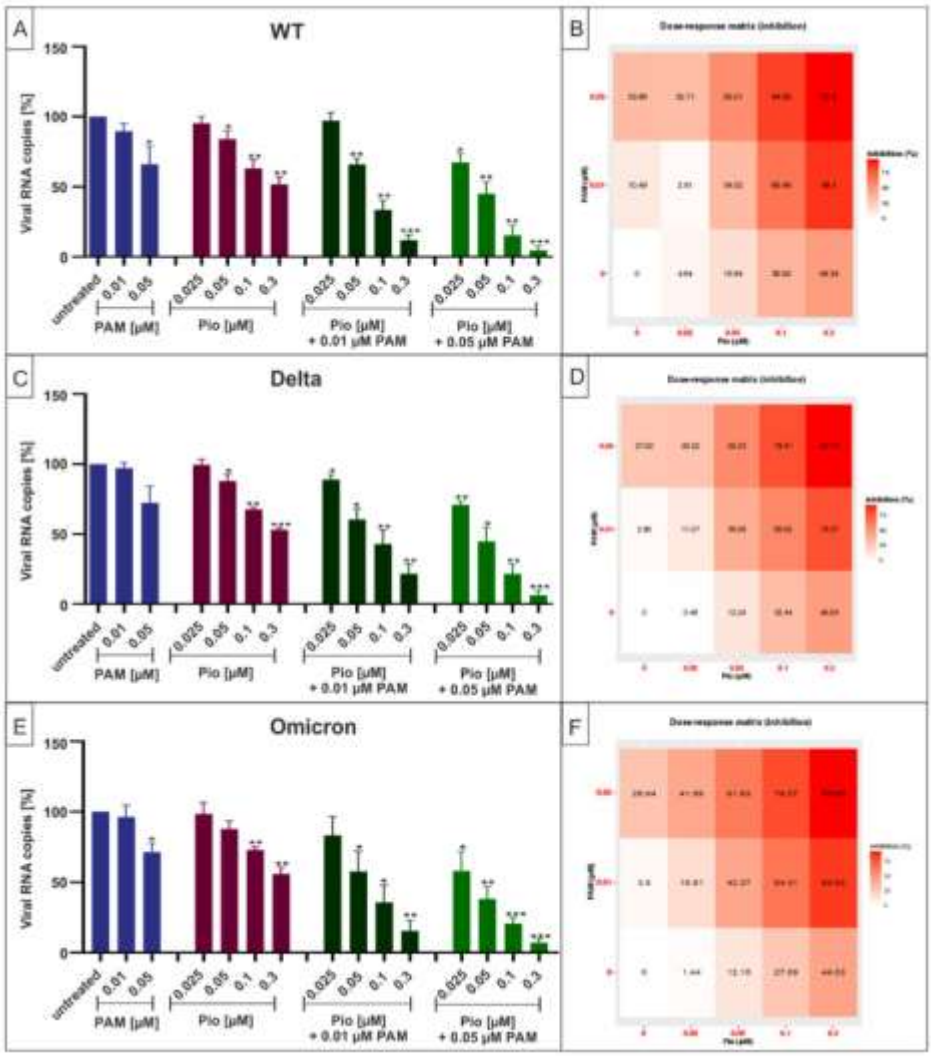
Exhibit 6: IC_{90} values of pamapimod and pioglitazone against SARS-CoV-2 Wuhan wild type and VOCs in Calu-3 cells

SARS-CoV-2 variant	Pamapimod IC_{90} concentration (µM)	Pioglitazone IC_{90} concentration (µM)
Wuhan wild type	~3	~10
Alpha	~3	~15
Beta	~3	~15
Gamma	~3	~15
Delta	~4	~12
Omicron	~3	~12

Source: Setz C, Große M, Auth J et al. Int J Mol Sci. 2022 Jun 20;23(12):6830. doi: 10.3390/ijms23126830 (Table 1)

A separate in vitro study was performed to assess whether the KIN001 combination could have synergistic antiviral activity. Calu-3 cells were infected with SARS-CoV-2 (either wild type, Delta or Omicron variants), then treated with different concentrations of pamapimod and pioglitazone, alone or combined. Following treatment with increasing concentrations of pioglitazone (25–300nM) in combination with either 10nM or 50nM of pamapimod, a significant dose-dependent reduction in SARS-CoV-2 replication capacity was observed across all the tested variants. This ranged from 10–88% (using 10nM pamapimod) and 27–95% (using 50nM pamapimod); see Exhibit 7. Modelling of the data revealed synergistic antiviral activity of the combination.

Exhibit 7: Antiviral activity of the combinatory treatment of pamapimod and pioglitazone following infection with SARS-CoV-2 Wuhan wild type, Delta and Omicron



Source: Setz C, Große M, Auth J et al. *Int J Mol Sci.* 2022 Jun 20;23(12):6830. doi: 10.3390/ijms23126830 (Figure 7)

The safety of KIN001 was evaluated in a three-month toxicity study in rats in accordance with good laboratory practice regulatory guidelines. The data showed no new findings from the combination versus the individual drugs.

Moving to the clinic with KINETIC and KINFAST trials

The Swiss government awarded Kinarus a grant of up to CHF7m to evaluate KIN001 as a treatment for COVID-19 in two Phase II studies. The first study, KINETIC (EudraCT No. 2020-005849-16), began in H221 and is an eight-week, double-blinded, randomised placebo-controlled Phase II study assessing the effects of four weeks of twice-daily KIN001 (total daily dose of 150mg

pamapimod and 10mg pioglitazone) in hospitalised COVID-19 patients. The primary objectives of the trial are to determine the efficacy of KIN001 to reduce mortality or severe respiratory failure. The company plans to enrol 430 patients across multiple sites in Europe and South America. The study successfully completed an initial safety analysis in April 2022 after the first 40 patients completed therapy, with the independent Data Safety and Monitoring Board recommending continuation of the study.

As of 6 June 2022, 130 patients were enrolled in KINETIC. Interim data following the assessment of c 130 patients is expected in late Q322, and top-line data are projected to be available in 2023.

KINFAST study

KINFAST, a second Phase II trial of KIN001, is designed to evaluate its potential to reduce the severity and duration of COVID-19 in ambulatory COVID-19 patients not requiring hospitalisation. KINFAST recently received regulatory authorisation in Switzerland and Germany and is expected to start in Q322. The trial is designed to include 430 patients, who will receive KIN001 for two weeks (at the identical dose as in the KINETIC trial), and the primary endpoint is the reduction of the severity of COVID-19 symptoms and time to recovery, as determined using patient-reported outcomes. We note that this endpoint of patient-reported outcomes data has been proposed and recommended by the FDA in its guidance to industry 'for sponsors initiating clinical trials evaluating drugs for the prevention or treatment of COVID-19 in outpatient adult and adolescent subjects'. Kinarus will perform an interim analysis to assess the preliminary efficacy and safety of KIN001 after approximately 130–150 patients have completed treatment and follow-up.

Altogether we believe the data from KINFAST and KINETIC will inform future development strategies for the product candidate in COVID-19, namely whether the best development path lies in hospitalised patients or those with less severe COVID-19 disease. Over 32 million COVID-19 cases were reported in the United States by the Centers for Disease Control and Prevention in H122, and more than 1.17 million US residents were hospitalised over this period. We estimate 1.5 million annual hospitalised cases in the EU5 (UK, France, Germany, Spain, Italy) based on Our World in Data statistics. We continue to expect that there will be an ongoing need for effective treatment options for at least the next several years, and possibly longer, and hence the revenue opportunity for clinically relevant and efficacious COVID-19 treatments could be significant.

The COVID-19 treatment landscape is expanding

A selected list of approved or authorised COVID-19 pharmacological treatments is presented in Exhibit 8. We note that Pfizer reiterated FY21 guidance of $22bn in FY22 Paxlovid sales in May 2022, and Merck raised FY22 Lagevrio sales guidance to $5.0–5.5bn in April 2022. Gilead reported that FY21 Veklury (remdesivir) sales were $5.6bn and $1.5bn in Q122 (+5% y-o-y). Beyond current antiviral therapies or other products (eg antibodies) targeting the virus itself, we reiterate that once oxygen supplementation or mechanical ventilation is required, anti-inflammatory drugs (eg dexamethasone) or immunomodulatory drugs (eg Janus kinase inhibitor baricitinib, or interleukin-6 antagonist tocilizumab or sarilumab) can be used.[7]

[7] In Europe, Kineret (anakinra), an interleukin-1 receptor antagonist, is also approved for hospitalised COVID-19 patients with pneumonia requiring supplemental oxygen.

Exhibit 8: Selected approved or authorised COVID-19 treatments

Product	Company	2021 global sales across all indications	Authorised use	Mechanism of action	Notes
Paxlovid	Pfizer	$76m*	Mild-to-moderate COVID-19 in adults and paediatric patients who are at high risk for progression to severe COVID-19.	Combination of nirmatrelvir, a novel main protease (Mpro) inhibitor and ritonavir, an antiretroviral medication. Paxlovid disrupts replication of SARS-CoV-2.	FDA's EUA based on EPIC-HR Phase II/III randomised, double-blind, placebo-controlled trial (NCT04960202, 2246 participants) results. Paxlovid reduced risk of hospitalisation/death by 88% within five days of symptom onset compared to placebo. Pfizer in May 2022 reaffirmed forecast $22bn in FY22 sales. EPIC-SR study in standard-risk COVID-19 patients did not meet primary endpoint of self-reported, sustained alleviation of all symptoms for four consecutive days, leading Pfizer to cease enrolment due to low rate of hospitalisation or death in this standard risk population.
Molnupiravir (Lagevrio)	Merck	$952m**	EUA in mild-to-moderate COVID-19 in adults who are at high risk of progressing to severe COVID-19, and for whom alternative treatment options are not accessible or appropriate.	Nucleoside analogue, which gets incorporated into growing viral RNA strands causing a point mutation, inhibiting SARS-CoV-2 replication.	MOVe-OUT Phase III trial (NCT04575597) of 1,734 enrolled participants showed superiority of molnupiravir vs placebo at interim analysis; risk of hospitalisation or death through day 29 was 7.3% compared with 14.1% for placebo. Merck in April 2022 forecast $5.0–5.5bn in FY22 Lagevrio sales.
Veklury (Remdesivir)	Gilead Sciences	$5,565m	Severe COVID-19 in hospitalised adults and paediatric patients. Also approved for mild-to-moderate COVID-19 in adults and paediatric patients who are at high risk for progression to severe COVID-19.	Antiviral prodrug that inhibits the RNA-dependent RNA polymerase (RdRp) enzyme in SARS-CoV-2 by competing with the typical counterpart, substrate ATP, during viral replication. This results in inhibition of viral RNA synthesis.	ACTT-1 trial (NCT04280705) on mild/moderate and severe COVID-19 showed median time to recovery was 10 days in Veklury group vs 15 days in placebo group. Study 5774 (NCT04292730) on moderate COVID-19 patients showed that patients who received 5-day Veklury course at day 11 had 65% improvement in outcome on 7-point ordinal scale compared to those receiving only SoC.
Baricitinib (Olumiant)	Eli Lilly and Incyte	$1,115m	Severe COVID-19 in hospitalised adults requiring supplemental oxygen, non-invasive/invasive mechanical ventilation, or ECMO (Extracorporeal Membrane Oxygenation).	Selective inhibitor of Janus kinases, JAK1 and JAK2, inhibiting the effect of IL-6 on the STAT3 pathway, reducing hyperinflammation. It may also inhibit endocytosis of SARS-CoV-2.	ACTT-2 trial, NCT04401579, showed that treatment with Veklury and baricitinib combination was superior to treatment with Veklury alone in reducing time to recovery within 29 days after randomisation (rate ratio of 1.16). In the COV-BARRIER study, NCT04421027, the 28-day all-cause mortality was 8% for baricitinib and 13% for placebo. Note that the product is also approved for non-COVID-19 indications (eg rheumatoid arthritis).
Actemra (Tocilizumab)	Roche (Genentech)	$3,900m (approx)	Severe COVID-19 in hospitalised adults and paediatric patients (two years or older) who are receiving corticosteroids and require supplemental oxygen, non-invasive ventilation or ECMO.	Immunosuppressive monoclonal antibody that reduces inflammation by blocking the IL-6 receptor.	In EMPACTA Phase III trial (NCT04372186), the cumulative percentage of patients who had received mechanical ventilation/died by day 28 was 12% vs 19.3% in the placebo group (128 patients). Note that the product is also approved for non-COVID-19 indications (including rheumatoid arthritis).
Evusheld (tixagevimab co-packaged with cilgavimab)	AstraZeneca	-	For emergency use as pre-exposure prophylaxis for prevention of COVID-19 in adults and paediatric individuals.	Combination of two long-acting antibodies (LAABs). Combined, these bind to two distinct sites on SARS-CoV-2 spike protein, preventing the virus from entering human host cells.	Phase III study, Provent (NCT04625725), enrolled 5,197 participants and found that it reduced risk of developing symptomatic COVID-19 by 77% vs placebo with protection from the virus continuing for at least six months.
Bebtelovimab	Eli Lilly	-	Mild-to-moderate COVID-19 in adults and paediatric patients at high risk of progressing to severe COVID-19, and for whom alternative COVID-19 treatment options are either not accessible or appropriate.	Monoclonal antibody shown to retain full neutralising activity against omicron variant and subvariants (including BA.2 subvariant). It binds to an epitope on the SARS-CoV-2 spike protein, blocking interaction between ACE2 and spike protein.	Granted EUA after Phase II BLAZE-4 trial (NCT04634409) on non-hospitalised patients who were treated with bebtelovimab (Beb) alone or together with bamlanivimab and etesevimab. 1,755 participants were enrolled. Of the low-risk patients, persistently high viral load (PHVL) occurred in 12% of patients treated with Beb vs 19.8% with the placebo.

Source: Edison Investment Research and various company websites and news releases. Note: Unless stated otherwise, authorisation in paediatric patients is for those aged 12 or older. *Pfizer reaffirmed forecast of $22bn in FY22 Paxlovid sales in May 2022. **Merck in April 2022 forecast $5.0–5.5bn in FY22 Lagevrio sales.

COVID-19 pipeline treatments

A summary of selected drug candidates targeting SARS-CoV-2, which would be direct competitors for KIN001 if approved, is presented in Exhibit 9. We believe sabizabulin (Veru) could be close to approval. The drug is designed to bind to the 'colchicine binding site' of a and b tubulin and inhibits tubulin polymerisation, resulting in both antiviral and anti-inflammatory activities. A Phase III trial (NCT04842747) evaluated daily 9mg oral doses of sabizabulin versus the placebo in hospitalised COVID-19 patients at high risk of developing acute respiratory distress syndrome (ARDS). Following a planned interim analysis, the independent data monitoring committee halted the study 'early for overwhelming efficacy' following a finding of a significant 55.2% mortality reduction in the intent-to-treat population. The company submitted an EUA application in June 2022.

Exhibit 9: Pipeline of potential targeted therapies for COVID-19

Product	Company	Stage/ Status	Mechanism of action	Notes
Sabizabulin	Veru	Phase III completed	Sabizabulin binds to the colchicine binding site of a and b tubulin, inhibiting tubulin polymerisation. This disrupts intracellular transport of SARS-CoV-2 and other viruses along microtubules.	Phase III trial (NCT04842747) in hospitalised patients with moderate to severe COVID-19 who are at high risk for ARDS. Interim analysis indicated that there was a statistically significant 55.2% mortality reduction in the intent-to-treat population. An EUA application was submitted in June 2022.
Lenzilumab	Humanigen	Phase III completed	Monoclonal antibody that binds to and neutralises GM-CSF.	The LIVE-AIR Phase III trial (NCT04351152) showed that the likelihood of survival of hospitalised COVID-19 patients without invasive mechanical ventilation to day 28 was significantly greater with lenzilumab, combined with SoC, than placebo. EUA application was not accepted by FDA. Top-line results from the subsequent Phase III ACTIV-5/BET-B (NCT04583969) study in hospitalised adults did not meet primary endpoint but showed a non-significant trend toward a reduction in mortality.
Tavalisse (Fostamatinib)	Rigel Pharma	Phase III ongoing	Fostamatinib selectively inhibits spleen tyrosine kinase (SYK), which is involved in the intracellular signalling pathways of a range of immune cells.	Phase II trial (NCT04579393) in hospitalised adults with COVID-19 showed that the addition of fostamatinib to SoC improved clinical outcomes compared to placebo. In February 2021 the Phase III trial (NCT04629703) commenced.
Adintrevimab (ADG20)	Adagio Therapeutics	Phase II/III ongoing	ADG20 is a human immunoglobulin (Ig)G1 monoclonal antibody that targets the SARS-CoV-2 spike protein. It is intended to impact viral replication and block viral entry.	EVADE (NCT04859517) is a placebo-controlled Phase III study evaluating ADG20 for prevention of COVID-19. Preliminary EVADE data indicated that ADG20 was associated with lower incidence of symptomatic COVID-19 vs placebo (1.6% vs 5.7%). STAMP Phase III trial (NCT04805671) is investigating ADG20 in mild-to-moderate COVID-19 patients at high risk of progression. Following in-vitro data suggesting less activity against Omicron BA.2, the company is pausing its EUA submission plan.
FP-025	Foresee Pharma	Phase II/III completed	FP-025 is a non-competitive inhibitor of MMP-12, a modulator of multiple components of the extracellular matrix, in particular elastin and collagen.	Phase II/III clinical trial (NCT04750278) completed but results are yet to be published.
Bemnifosbuvir (AT-527)	Atea Pharma	Phase II (failed primary endpoint)	AT-527 is a guanosine nucleotide analogue polymerase inhibitor that may interact with both the RNA-dependent polymerase (RdRp) and NiRAN active sites on the SARS-CoV-2 RNA polymerase. This may inhibit viral replication.	In top-line analysis of data from Phase III MORNINGSKY trial (NCT04889040) in non-hospitalised patients with mild or moderate COVID-19, the primary endpoint, time to symptom alleviation, was not achieved. However, a 71% reduction in hospitalisation rate was observed in the AT-527 arm (n=137) vs placebo (n=70). Currently discussing next steps in the development program.
Bemcentinib	BerGenBio	Phase II completed	Bemcentinib is an AXL receptor tyrosine kinase inhibitor that may prevent viral intracellular entry and augment the type 1 interferon response, a key antiviral defence mechanism	Two separate Phase II studies, BCBC020 (n=115) and ACCORD2 (n=61), of bemcentinib in addition to SOC in hospitalised COVID-19 patients showed that the pooled bemcentinib arm had a survival rate of 96.5% vs 91.2% for SOC alone. Bemcentinib's efficacy will be tested in adaptive platform trial program (EU-SolidAct) commencing in H222.

Source: Edison Investment Research and various company websites and news releases.

KIN001's potential positioning given competitive landscape

The COVID-19 treatment market remains broad, and the choice of treatment varies by disease stage. As stated above, antivirals or products targeting the virus SARS-CoV-2 itself (like Paxlovid and Lagevrio) can be effective when given in earlier courses of the disease but are not indicated in the more severe disease stages where treatments to modulate or control the disease's resulting inflammatory and/or fibrosis-inducing reactions become necessary. As shown by Exhibit 9, a

majority of the later-stage COVID-19 drug candidates in therapeutic development are targeting hospitalised patients with more severe levels of disease. KIN001's multifaceted mechanism of action, where it has shown antiviral, anti-inflammatory and anti-fibrotic effects, could provide therapeutic effectiveness across both the earlier and later stages of the disease (excluding the most severe disease stages where mechanical oxygen or intubation is required).

As stated above, we believe the data from KINFAST and KINETIC will inform future development strategies for the product candidate in COVID-19, namely whether the best development path lies in hospitalised patients or those with less severe COVID-19 disease.

Idiopathic pulmonary fibrosis opportunity

KIN001's third targeted indication is IPF, a progressive disease that leads to lung scarring and fibrosis that hampers the lungs' ability to adequately transport oxygen. IPF is one of the most common forms of interstitial lung diseases (ILDs), and symptoms include shortness of breath, a persistent dry cough and fatigue. Mean survival is only three to five years following diagnosis. IPF has an estimated global prevalence of 13–20 per 100,000 people, with approximately 100,000 people affected in the United States and an annual US incidence of c 30,000–40,000.

Only two approved medications for IPF

There are currently only two approved drugs for IPF, Ofev (nintedanib, Boehringer Ingelheim, $2.9bn in 2021 sales) and Esbriet (pirfenidone, Roche, $1.1bn in 2021 sales), although pirfenidone has recently gone generic. According to consensus estimates at Evaluate Pharma, global IPF therapeutics sales are projected to increase from $4.1bn in 2021 to $5.8bn in 2024, but then decrease to $1.7bn in 2028 following Ofev's expected patent expiry in 2025. We believe there is significant unmet need as both approved drugs have had high rates of discontinuation due to adverse events and tolerability issues (Exhibit 10).

Exhibit 10: Marketed IPF products

Drug	Company	Target	Administration	2021 sales	Approximate cost	Patent expiry	Efficacy	Toxicities
Ofev (nintedanib)	Boehringer Ingelheim	Inhibition of multiple receptor tyrosine kinases, including growth factor receptors such as FGFR, PDGFR and VEGFR	Oral, 150mg twice daily	$2.949bn	$12,400 for 60 capsules, or monthly supply (take two daily)	US 30/09/25 Ex US 21/02/24	45–52% reduction in annual rate of forced vital capacity (FVC) decline vs placebo in two Phase III trials	Diarrhoea, nausea, abdominal pain, vomiting, liver enzyme elevation and weight loss
Esbriet (pirfenidone)	Roche	Not fully established; may inhibit collagen synthesis and reduce fibroblast proliferation and stimulation	Oral, 267mg, three capsules taken together, at three times per day (nine total capsules per day)	$1.137bn	$11,000 for 270 capsules, or monthly supply (take nine daily)	US 15/10/21 Ex US 28/02/21	28–52% reduction in FVC decline after 48 weeks across three Phase III trials	Nausea, rash, abdominal pain, fatigue, dyspepsia, photosensitivity and weight loss

Source: FDA, Drugs.com

Both nintedanib and pirfenidone have been shown to reduce the rate of lung function decline (measured by forced vital capacity, or FVC) by up to around 50%. Pirfenidone has been associated with improvement of all-cause mortality, whereas nintedanib has shown trends (but not reaching statistical significance) towards this. Both approved treatments have significant side effects/toxicities (see Exhibit 10) that lead to high rates of discontinuation.

A recent study investigated the discontinuation profiles of pirfenidone and nintedanib in patients with IPF; the discontinuation rates within one year of antifibrotic treatment were statistically similar for both nintedanib and pirfenidone (50% vs 48.5%). Discontinuation rates were marginally higher for pirfenidone (81.3%) than nintedanib (68%) in patients over a three-year observation period.

Preclinical data support KIN001 investigation for IPF

The combination of pamapimod and pioglitazone in KIN001 is proposed to reduce both inflammation and fibrosis in IPF. Preclinical proof-of-concept has been demonstrated by the company in a 21-day IPF mouse model where fibrotic lung injury was induced by bleomycin (an antibiotic anti-tumour agent). In this study, pioglitazone and pamapimod individually and combined were dosed and lung fibrosis status was investigated using an eight-point Ashcroft score three weeks after bleomycin administration. Pamapimod and pioglitazone each reduced the fibrosis score, although the combination resulted in a greater reduction in fibrosis compared to either drug alone. KIN001 also was more efficacious in comparison to a pirfenidone comparator arm. The triple combination of pamapimod, pioglitazone and pirfenidone resulted in the lowest Ashcroft score, suggesting possible additive KIN001 effects on top of the current SoC.

Exhibit 11: Effect of KIN001 on lung fibrosis score versus pioglitazone, pamapimod and pirfenidone (Esbriet)

Source: Kinarus Therapeutics KOL webcast presentation, 2022

To understand the KIN001 mechanisms of action, gene expression changes in lung tissue from the bleomycin study, were measured by RNAseq. The data demonstrated that the KIN001 combination of pamapimod/pioglitazone has synergistic effects in the animal model to downregulate numerous interleukin/interleukin receptor, TNF/TNF receptor and chemokine/cytokine mRNAs in comparison to the effects of the single agents.

Kinarus intends to initiate a 12-month randomised, double-blinded Phase II trial for KIN001 (oral pamapimod 150mg with pioglitazone 30mg) in IPF patients, in Q123. This Phase II trial is anticipated to enrol a cohort of c 75 patients in total (c 50 for KIN001 arm versus c 25 in placebo arm) in Switzerland and potentially other countries as well. The primary objective will be to assess lung function in terms of mean absolute change from baseline in FVC at 52 weeks and is powered to show a 40% improvement.

With the wide range of adverse effects from the two approved treatments and high discontinuation rates, we believe KIN001 could obtain material market share if it demonstrates a superior therapeutic profile (ie delivering a comparable improvement in lung function with an improved adverse event profile). However, we caution that the emergence of generic versions of both pirfenidone (2022) and Ofev (expected in 2025) may result in pricing pressure for KIN001 (and other emerging IPF treatments) and/or limit its potential market share if approved. The extent of market share captured by KIN001 will also depend on its therapeutic profile versus the existing approved drugs or potential competitors. Currently, pricing pressure has been modest with generic pirfenidone priced at a c 10% discount to Esbriet.

IPF: Competitive landscape

We note that several IPF drug candidates are in development, with trial data suggestive of significant reductions in FVC decline. A selected list of later-stage candidates is shown below.

Exhibit 12: Selected later-stage candidates in development for IPF

Drug	Company	Mechanism	Administration	Status	Efficacy	Comments
Pamrevlumab (FG-3019)	FibroGen	mAb inhibiting Connective tissue growth factor	IV every three weeks	Phase III	Phase II trial (NCT01890265): 103 randomly assigned patients. Pamrevlumab reduced decline of predicted FVC by 60.3% at week 48.	Drug appears to show a relatively good safety profile to date. Two ongoing Phase III trials, NCT04419558 (Zephyrus II) and NCT03955146 (Zephyrus-I), with Zephyrus-I data expected in 2023.
PRM-151 (RG-6354)	Roche (through Promedior acquisition)	Macrophage polarisation factor agonist designed to prevent and possibly reverse fibrosis	IV infusion, three times in first week and then every four weeks	Phase III	48% reduction in FVC decline at 24 weeks in 117-patient Phase II trial and stabilisation in 6-minute walk test. Extension results shown here.	Promedior was bought by Roche for $390m upfront and up to $1bn in milestones after the Phase II data.. Ongoing Phase III trial Starscape (NCT04552899). Roche expects to launch in 2024.
Tyvaso (treprostinil)	United Therapeutics	A prostacyclin analogue designed to promote vasodilation and inhibit platelet aggregation	Inhale up to 12 breaths, four times daily	Approved in pulmonary hypertension. Phase III in IPF	Phase II/III study in ILD complicated by pulmonary hypertension evaluated efficacy of 16 weeks of treatment of Tyvaso vs placebo in 326 adults. Compared to placebo Tyvaso was associated with a 42.4% reduction in proportion of patients with >=10% FVC decline.	Ongoing Phase III trial (Teton), NCT04708782) studying its efficacy over 52-week period in patients with IPF.
GLPG-1205	Galapagos	G-protein-coupled receptor 84 (GPR84)	Oral, 100mg once daily	Phase IIb (discontinued)	GLPG-1205 55% reduction in FVC decline at week 26 in 68-patient Phase II trial in patients SoC + either drug or placebo. Results did not show statistical significance.	Galapagos discontinued GLPG-1205 from development pipeline in a cost-cutting exercise in H121 and plans to start Phase II on GLPG4716
BI 1015550	Boehringer Ingelheim	Phosphodiesterase 4B (PDE4B) inhibitor	Oral, 18mg twice daily	Phase III	Over 12-week treatment period (n=147) the median change in FVC in patients who were not on approved antifibrotics was +5.7mL vs -81.7mL for placebo.	The drug received FDA breakthrough therapy designation. Phase III expected to commence later this year (NCT05321069).
TAS-115 (pamufetinib)	Otsuka Holdings	Multi-kinase inhibitor (PDGFR, VEGFR and M-CSF)	Oral, 200mg once daily	Phase II being developed in Japan	Treatment repeated for 13 weeks/or up to 26 weeks. 77% of patients who completed 13-week administration showed attenuation of FVC decline.	Development plan for North American or European markets unspecified.
INOpulse	Bellerophon Therapeutics	Medical device/delivery system to deliver nitric oxide via inhalation	Pulsed inhaled nitric oxide (iNO 45 µg/kg)	Phase III in fibrotic ILD	In Phase II trial with 44 patients (30 iNO45 and 14 placebo) requiring oxygen, a clinical benefit of 12.3 min/d increase in MVPA (moderate to vigorous physical activity) was observed in iNO45 group.	Ongoing Phase III trial, REBUILD, (NCT03267108, n=300); study to assess efficacy of pulsed inhaled nitric oxide (iNO) in patients at high risk of pulmonary hypertension who are on long-term oxygen therapy.

Source: Edison Investment Research plus various company websites and news releases.

We highlight that pamrevlumab (FibroGen) appears to be a promising potential IPF treatment based on the data from its 103-patient Phase II trial, in which pamrevlumab reduced the rate of FVC decline versus placebo by approximately 60% at the 48-week mark. Data from the first Phase III study (Zephyrus-I) is expected in 2023. Pamrevlumab is administered by intravenous infusion every three weeks.

We are also monitoring PRM-151 (RG-6354), also delivered by intravenous infusions, which is being developed by Roche following its acquisition of Promedior. In a 117-patient Phase II trial, PRM-151 demonstrated a 48% reduction in FVC decline versus placebo at 24 weeks. Roche initiated a 658-patient Phase III trial (Starscape) for the programme, and it is anticipating to launch the drug in IPF in 2024. And finally, in terms of oral IPF drug candidates, we are monitoring BI1015550 (Boehringer Ingelheim), a PDE4B inhibitor, which was granted Breakthrough Therapy Designation by the FDA. In a recent Phase II study, BI1015550 actually showed an increase in FVC (albeit it was only measured at 12 weeks), rather than just a slower rate of decline. A Phase III study is planned to start in H222.

Financials

Kinarus Therapeutics became public through a reverse takeover transaction of the privately held Kinarus AG by Perfect Holding SA in June 2022. Exhibit 14 shows the audited 2020 financials of Kinarus AG and the pro forma unaudited 2021 financials of the combined company (Kinarus Therapeutics), although pro forma FY21 cash flow statements were not provided. Kinarus AG's FY21 EBITDA loss was CHF4.7m, and the pro forma FY21 statement showed a combined EBITDA loss of CHF5.1m. R&D expenses (for both Kinarus AG and Perfect Holding SA) were CHF1.7m in FY21.

Kinarus AG had an FY21 FCF burn rate of CHF1.1m, but this included a CHF4.4m prepayment from the Swiss government (as part of the COVID-19 grant described above). Excluding this payment, the normalised burn rate would have been CHF5.5m.

Kinarus AG had CHF5.3m in cash and equivalents at 31 December 2021 (vs CHF0.1m for Perfect Holding SA). Kinarus reported a pro forma end FY21 gross cash position of CHF8.8m, which also includes the CHF3.4m raised in a Series B financing round in February 2022 as if it were already in the pro forma balance sheet. Kinarus also has CHF3m in interest free debt on its balance sheet, guaranteed by third parties (90% by the Canton of Basel-Stadt) and due in 2025. Altogether, Kinarus Therapeutics had end December 2021 pro forma debt of CHF3.5m, resulting in an FY21 pro forma net cash position of CHF5.3m.

If we assume the company's FY22e FCF burn rate is similar to Kinarus AG's FY21 normalised rate (CHF5.5m), we would expect the company's funds on hand to last into mid-2023, although this could be extended a few months further if the company receives the remaining CHF2.6m from the Swiss government grant. Kinarus in August 2022 announced an agreement with an entity managed by Yorkville Advisors, whereby the company may raise up to CHF20m in convertible notes, to be drawn in tranches, over the next 36 months. Kinarus may issue convertible notes tranches as part of the arrangement at its own discretion, subject to certain conditions. The unsecured convertible notes each have a term of six months and pay interest at a 4% annualised rate. The notes are convertible into Kinarus shares and the conversion would be the lower of:

1. 120% of the volume-weighted 10-day trading price of Kinarus shares prior to the company's decision to issue the convertible notes, or
2. 92% of the lowest daily volume-weighted trading price of Kinarus shares in the 10 days prior to conversion.

We believe this facility may be used to support the funding needs of its planned KIN001 clinical trials in wet AMD and IPF. Once these studies begin, the company's burn rate is likely to increase. Kinarus has guided that it expects its total expenditures, assuming all these studies are underway, will be between CHF20m and CHF25m between mid-2022 and year-end 2024.

Exhibit 13: KIN001 development plan, value inflection points and financing need

Source: Kinarus Therapeutics

Potential catalysts

Progression of the company's three programmes and successful outcomes could drive potentially value-generating monetisation or product licensing/partnership event/outcomes, and/or support future financing rounds to further fund the pipeline's internal development.

As shown above in Exhibit 13, Kinarus has outlined its timelines and projected financial needs and has identified what it considers to be potential strategic value inflection points. It expects to report interim KINETIC data in late Q322 and top-line data by mid-2023. The KINFAST ambulatory COVID-19 study, due to start in Q322, is expected to provide data in or around mid-2024. Both studies combined should cost c CHF9m, net of the total grant funding (CHF7m) from the Swiss government. The Phase II wet AMD study, with an expected cost of CHF5m, could start in Q422 and report top-line data in H224. The Phase II IPF study is currently anticipated to start in Q123 and complete in or around year-end 2024.

Sensitivities

Kinarus is subject to the usual risks associated with drug development including clinical development delays or failures, regulatory risks and competitor successes. Kinarus will need to raise significant capital to continue KIN001 development until commercialisation or a major market licensing transaction. The company may face significant dilution if funding needs are met through equity issuances and/or convertible debt, and while a portion of funding needs may be met via non-convertible debt, we believe this is less likely and we note that rising interest rates may pose a challenge to the availability and cost of such potential debt.

We recognise that there is little in-human proof-of-concept data for KIN001 at this stage. The realisation of such proof-of-concept could drive a re-rating in the company's valuation and/or facilitate strategic transactions. However, the failure to show proof-of-concept efficacy could jeopardise future business development prospects for KIN001.

Kinarus faces high product concentration risk given that it is singularly focused on a single drug candidate, where a setback in its development could have a substantial effect on the company's pipeline and valuation. Concerns about pioglitazone's possible association with the development of bladder cancer may also influence prescribing behaviour for its use in long-term therapy (eg wet

AMD or IPF) if the drug is approved. To our knowledge, no country other than France has limited the use of pioglitazone for the chronic treatment of T2D.

With regards to the wet AMD indication, if KIN001 is successfully commercialised, it may be the first oral treatment for this indication. Substantial educational outreach to insurers, medical professionals and patients may be required to achieve significant market uptake and to inform these stakeholders of the benefits of long-term KIN001 usage, namely the expected reduction in anti-VEGF IVT agent dosing frequency. In IPF, Esbriet (pirfenidone) now having gone generic and Ofev's patent expiring in 2025 may limit KIN001's peak pricing potential and/or increase the hurdle to gain significant market share.

Exhibit 14: Financial summary

CHF000s	2020	2021
Year end 31 December	IFRS	IFRS
PROFIT & LOSS		
Revenue	0	0
Cost of Sales	0	0
Gross Profit	0	0
Sales, General & Administrative	(1,206)	(3,042)
Net Research & Development	(277)	(1,709)
Other operating expenses	(38)	(375)
EBITDA	(1,521)	(5,126)
Amortisation of intangible assets	0	(8,556)
Depreciation & other	(1)	(4)
Normalised Operating Profit (ex. amort, SBC, except.)	(1,522)	(5,130)
Operating profit before exceptionals	(1,522)	(13,686)
Exceptionals including asset impairment	0	0
Other	0	0
Reported Operating Profit	(1,522)	(13,686)
Net Finance income (costs)	(0)	263
Profit Before Tax (norm)	(1,522)	(4,867)
Profit Before Tax (FRS 3)	(1,522)	(13,423)
Tax	0	327
Profit After Tax and minority interests (norm)	(1,522)	(4,540)
Profit After Tax and minority interests (FRS 3)	(1,522)	(13,096)
Average Basic Number of Shares Outstanding (m)	4.9	1,096.1
EPS - normalised (£)	(0.31)	(0.00)
EPS - normalised and fully diluted (£)	(0.31)	(0.00)
EPS - (IFRS) (£)	(0.31)	(0.01)
Dividend per share (€)	0.0	0.0
BALANCE SHEET		
Fixed Assets	1,802	81,860
Intangible Assets	1,800	52,100
Tangible Assets	2	29,760
Investments in long-term financial assets	0	0
Current Assets	468	8,861
Short-term investments	0	0
Cash	419	8,800
Other	49	61
Current Liabilities	(983)	(2,311)
Creditors	(283)	(2,311)
Short term borrowings	(700)	0
Long Term Liabilities	0	(14,366)
Long term borrowings	0	(3,429)
Other long term liabilities	0	(10,937)
Net Assets	1,287	74,044
CASH FLOW STATEMENT		
Operating Income	(1,522)	
Movements in working capital	(34)	
Net interest and financing income (expense)	(0)	
Depreciation & other	1	
Taxes and other adjustments	253	
Net Cash Flows from Operations	(1,302)	
Capex	0	
Acquisitions/disposals	0	
Interest received & other investing activities	0	
Net Cash flows from Investing activities	0	
Net proceeds from share issuances	1	
Net movements in long-term debt	700	
Dividends	0	
Other financing activities	0	
Net Cash flows from financing activities	701	
Effects of FX on Cash & equivalents	0	
Net Increase (Decrease) in Cash & equivalents	(600)	
Cash & equivalents at beginning of period	1,019	
Cash & equivalents at end of period	419	
Closing net debt/(cash)	281	5,371
Lease debt	0	0
Closing net debt/(cash) inclusive of IFRS16 lease debt	281	5,371
Free cash flow	(1,302)	

Source: Kinarus Therapeutics AG; Note: 2020 accounts reflect statements of privately held Kinarus AG and 2021 statements represent pro forma financials of Kinarus Therapeutics AG following reverse merger transaction with Perfect Holding

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia