Molecure

Novel approaches for problematic diseases

Molecure aims to discover and develop drugs that have novel mechanisms of action to address serious unmet medical needs. Its two lead assets, OATD-01 and OATD-02, are approaching important clinical development milestones. After a strategic decision by partner Galapagos (June 2022), the rights to OATD-01 were returned to the company. Molecure now plans to leverage newly collected data to commence a Phase II trial in sarcoidosis in mid-2023, with top-line results expected in Q125. In addition, management anticipates OATD-02 could enter Phase I trials in solid tumour indications in Q422, subject to regulatory approval. With a cash position of PLN80.7m at end-September 2022, the company guides that its current runway is into Q224.

Focus on novel mechanisms of action

Molecure's key asset, OATD-01, is a chitotriosidase (CHIT1) inhibitor being developed in sarcoidosis. However, we believe the drug could also have commercial potential in other fibrotic indications, such as IPF or possibly NASH, if it can demonstrate a disease-modifying profile. In addition, OATD-02, a novel arginase-1/-2 (ARG1/2) inhibitor, has demonstrated the potential to restore the body's immunological response to tumours in preclinical studies.

Return of OATD-01 presents an opportunity

The return of the development rights to OATD-01 from Galapagos presents a considerable opportunity for Molecure, in our view. Despite a two-year development delay following the 2020 deal with Galapagos, the company has benefited from additional data generated by Galapagos as well as its PLN125m (US$28m) upfront licensing payment. Molecure will now continue to develop OATD-01 in sarcoidosis, an indication with substantial unmet medical need. If a disease-modifying effect is demonstrated, we see potential in other interstitial lung diseases (ILD) such as IPF.

Funding into Q224

With a net cash position of PLN80.7m at end-September 2022, management's expected cash runway sees the company funded to into Q224. However, top-line results from the Phase II trial in sarcoidosis, a major inflection point for Molecure, are expected in H125. Management is exploring non-dilutive funding options, but we expect the company will need to raise additional funds to complete Phase II development.

Historical Figures

Year end	Revenue (PLNm)	EBIT (PLNm)	EPS* (PLN)	DPS (PLN)	P/E (x)	Yield (%)
12/20	124.9	73.7	4.64	0.0	3.08	N/A
12/21	1.2	(13.6)	(0.98)	0.0	N/A	N/A

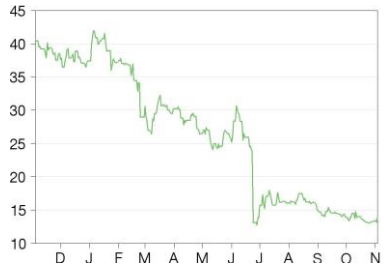
Source: Company accounts. Note: *EPS are diluted.

Pharma and biotech

7 November 2022

Price	PLN14
Market cap	PLN196m

Share price graph



Share details

Code	MOC
Listing	Warsaw Stock Exchange
Shares in issue	14.03m
Cash at 30 September 2022	PLN80.7m

Business description

Molecure is a clinical-stage biotechnology company. It uses its medicinal chemistry and biology capabilities to discover and develop first-in-class small molecule drug candidates that directly modulate the function of RNA and underexplored protein targets designed to treat multiple incurable diseases.

Bull

- Two assets to enter clinical development by end-FY23.
- OATD-01 has potential for disease-modifying action in interstitial lung disease.
- Pipeline supported by preclinical assets and technology platform.

Bear

- Delays or disruptions to timelines could affect management's estimated cash runway.
- Unvalidated mechanisms of action increase development risk.
- Additional funding needed to complete Phase II development.

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Molecure is a research client of Edison Investment Research Limited

Overview: Novel drugs with new mechanisms of action

Molecure (renamed from OncoArendi in Q122) is a Polish biotechnology company focused on the development of novel drugs that target underexplored pathways in diseases with significant unmet medical need. Currently, the company's most advanced clinical asset is CHIT1 inhibitor OATD-01, for which the worldwide rights were returned to the company in June 2022 after a strategic review by partner Galapagos. Positive safety and biomarker data from a Phase Ib trial of OATD-01 was reported in September 2020 and the company now expects to begin a Phase II trial investigating the drug's use in the treatment of sarcoidosis in mid-FY23. If OATD-01 can demonstrate a disease-modifying profile in Phase II trials, we see a significant opportunity in sarcoidosis and fibrotic indications such as idiopathic pulmonary fibrosis (IPF). For OATD-01, we expect Molecure's strategy will likely revolve around demonstrating clinically meaningful anti-granulomatous activity in sarcoidosis with the intention of out-licensing the asset for further development in other conditions such as IPF, non-alcoholic steatohepatitis (NASH) or inflammatory bowel disease (IBD), for which preclinical data suggests OATD-01 may be applicable. Newly acquired positive drug-drug interaction data obtained by Galapagos in the context of IPF has provided further encouragement in this indication.

Further, management expects to progress its ARG1/2 inhibitor OATD-02 into a first-in-human Phase I trial for the treatment of solid tumours in Q422. In our view, OATD-02's development may follow a similar strategy to OATD-01's: regional (Polish) Phase I trials followed by international, proof-of-concept Phase II studies, with the company aiming to out-license further development and commercialisation in oncology. Molecure is also developing multiple preclinical projects and a proprietary small molecule mRNA platform which, based on recent deals for similar platforms, we believe could be a significant future value driver for the company.

Financials: Funded into Q224, costs expected to increase

Molecure reported total operating costs of PLN9.00m and PLN21.2m in total cash outflows in the first nine months of 2022, as it continued to progress its pipeline and one-off costs from rebranding were recorded. Management intends to be running two parallel clinical trials by end-FY23 (OATD-01 Phase II and OATD-02 Phase I) and expects cumulative expenditure over H222 and FY23 will increase dramatically to reach PLN58m. At end-September 2022 Molecure reported a cash position of PLN80.7m (US$16.9m), which it expects will sufficiently fund planned operations into Q224. Management is also exploring various sources of non-dilutive funding in the form of grants and collaborative agreements, which in total the company estimates could potentially fund 30–50% of costs. Further information on financials is provided on page 12.

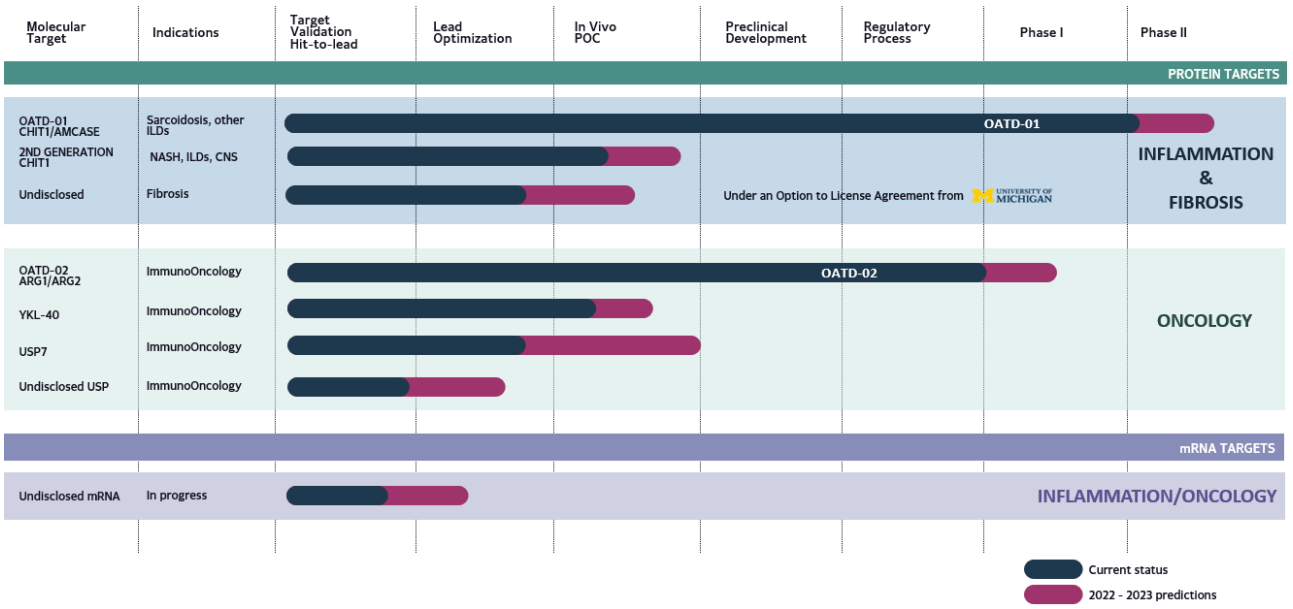
Sensitivities: Development and partnering

Molecure is subject to the normal risks associated with a pureplay biotechnology company. Primarily, the company is subject to risks associated with the clinical development of OATD-01 and OATD-02. Failure to meet clinical trial endpoints and/or delays in development timelines could have a material impact on the company's market value. Molecure is focused on targeting new disease pathways, meaning that OATD-01's and OATD-02's mechanisms of action are unvalidated in a clinical setting, which increases development risk for the company. Failure to demonstrate clinical proof-of-concept for OATD-01 in Phase II trials (results expected in H125) represents a significant medium-term risk and would likely cause the company to revaluate its long-term development timelines. As management's estimated cash runway will fund the company into Q224, the company will need to raise additional funds to complete OATD-01's Phase II trial. While Molecure is exploring non-dilutive funding options, capital may be raised through an equity offering, which could result in the significant dilution of existing shareholders.

A portfolio of novel assets

Molecure's portfolio (Exhibit 1) is focused on two key areas: inflammation and fibrosis; and oncology. While the company possesses a burgeoning discovery and preclinical pipeline, management's attention remains focused on the clinical development of OATD-01 and OATD-02 in sarcoidosis and solid tumour indications, respectively. OATD-01 is a novel, first-in-class chitinase inhibitor that the company is currently developing for the treatment of sarcoidosis but has potential applications in other inflammatory and fibrotic diseases (IPF, non-alcoholic steatohepatitis (NASH)). Positive Phase I safety and pharmacodynamic data, gathered from healthy volunteers, and a significant amount of animal model data support the commencement of a Phase II trial for the treatment of sarcoidosis in Q2/Q323. We expect the second asset, OATD-02, to enter clinical development in Q422 for the treatment of solid tumours. OATD-02 is a dual ARG1/2 inhibitor that the company believes could restore anti-tumour immune activity in oncology indications as a monotherapy and in combination with immune checkpoint inhibitors (anti-PD-(L)1 antibodies).

Exhibit 1: Molecure's pipeline



Source: Molecure corporate presentation July 2022

Molecure is also developing an innovative small molecule mRNA-targeting platform. Based on unique bioinformatics algorithms, this platform, the company asserts, allows expedited hit-optimisation for molecules that interfere and bind to specific mRNA structures, disrupting the gene translation process. Management expects that this platform will deliver over 20 hit compounds for in vitro proof-of-concept studies by Q423. Similar RNA targeting platforms have been the subject of considerable partnership deals with global pharmaceutical companies in recent years (eg Arrakis Therapeutics, Ribometrix and Skyhawk). Hence, if Molecure can deliver functioning and validated mRNA-targeting compounds in Q223, we expect this could lead to sizeable partnerships deals and/or contracts.

Molecure's strategy of pursuing novel mechanisms of action (chitinase and arginase inhibition) in areas of unmet medical need, in our view, offers the potential for significant commercial opportunity, if assets meet proof-of-concept thresholds in clinical trials. Despite the company having supportive mouse model data, the mechanisms currently under investigation (CHIT1, ARG1/2 inhibition) are not clinically validated in humans (currently no chitinase or arginase inhibitors are approved). We therefore see increased potential development risks compared to better-established mechanisms of action.

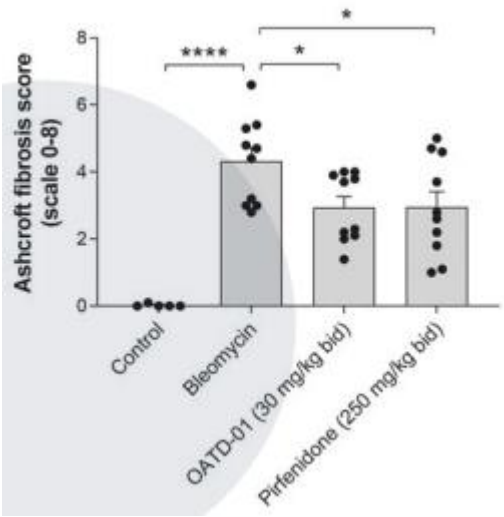
OATD-01: A first-in-class chitinase inhibitor

Molecure's previous partner for OATD-01, Galapagos (GLPG:AEX), returned the global rights for the CHIT1 inhibitor to the company in June 2022 following a shift in corporate strategy and a portfolio review. The drug was returned to Molecure with new drug-drug interaction (DDI) data from two independent studies involving standard-of-care drugs in IPF (nintedanib, pirfenidone) and midazolam. We expect the company will submit clinical and preclinical data to the regulators for the drug's use in sarcoidosis to support clinical development in this indication. Molecure believes advancing OATD-01 in sarcoidosis initially rather than IPF will provide a higher chance of success, where biological and functional endpoints are somewhat easier to assess. If Phase II trials in sarcoidosis demonstrate proof-of-concept for OATD-01 as an effective agent, we expect it would also make the asset more appealing to potential licensing partners, which may look to develop it in other interstitial lung diseases (eg IPF). Subject to regulatory approval, the company intends to commence a Phase II trial in sarcoidosis patients with OATD-01 in mid-2023.

Addressing inflammation and fibrosis with OATD-01

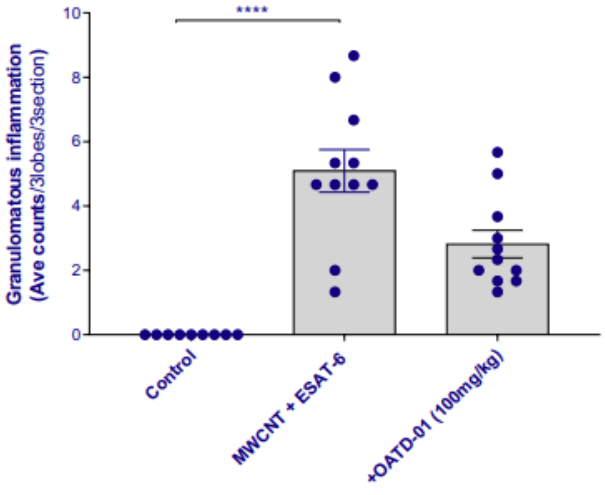
Management believes OATD-01 is a potent (IC_{50} human CHIT1 = 26nM) small molecule inhibitor of CHIT1, a human chitinase enzyme that is implicated in the body's immune response. Pathologically activated immune cells, such as macrophages and neutrophils, secrete CHIT1 as part of the body's natural immune response, thus the enzyme's activity is associated with inflammatory and fibrotic processes. OATD-01 is a first-in-class chitinase inhibitor developed by Molecure to be taken as a once-a-day pill for the treatment of inflammatory and fibrotic conditions. Preclinical studies, conducted by Molecure, have demonstrated OATD-01's ability to reduce fibrosis (measured by the Ashcroft fibrosis score) in mice with induced lung fibrosis (through exposure to bleomycin). In these experiments, OATD-01 showed a reduction in fibrosis on a comparable scale to a leading IPF drug (pirfenidone, Exhibit 2). In addition, OATD-01 been shown to reduce granulomatous inflammation in an induced sarcoidosis mouse model (Exhibit 3). Here, the combination of multi-walled carbon nanotubes (MWCNT) and early secreted antigenic target 6Da (ESAT-6) peptide induced granulomatous inflammation.

Exhibit 2: OATD-01 effect in lung fibrosis mouse model



Source: Molecure corporate presentation. Note: Bleomycin induces fibrosis.

Exhibit 3: OATD-01 effect in sarcoidosis mouse model



Source: Molecure corporate presentation. Note: MWCNT = multi-walled carbon nanotube, ESAT-6 = early secreted antigenic target 6KDa. MWCNT + ESTA-6 combination induces sarcoidosis.

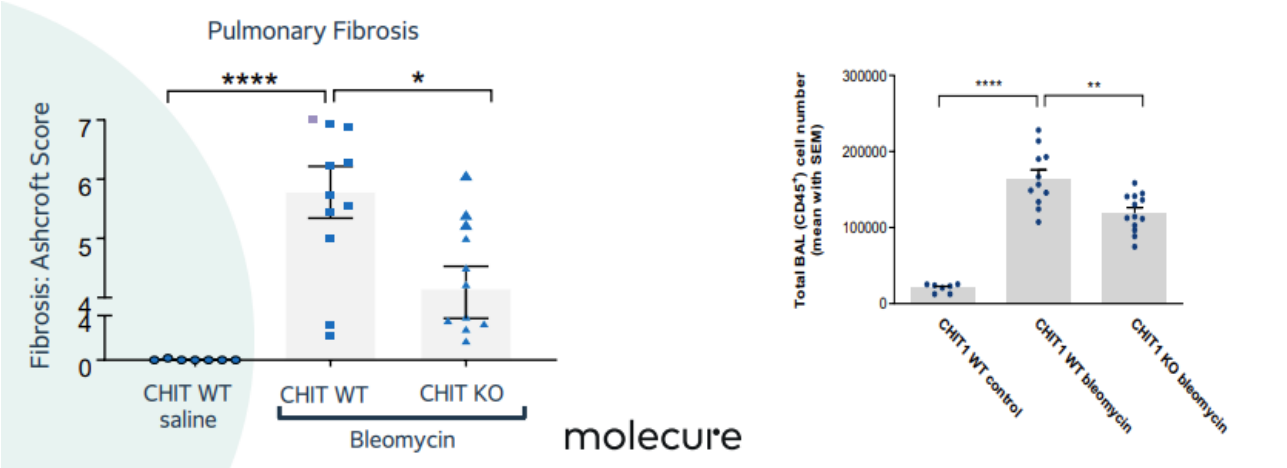
In our view, these data represent encouraging support for OATD-01's use in fibrotic and inflammatory lung conditions. However, we note that animal data are not directly comparable to humans. Molecure believes that this animal model data combined with CHIT1's specific action in

the development of fibrosis makes OATD-01 a potentially disease-modifying agent in fibrotic disease. The drug has so far demonstrated a good safety profile in Phase I studies and has received an orphan drug designation (ODD) for its use in sarcoidosis and IPF, which could provide the company with up to seven years of market exclusivity (post approval) for OATD-01 in each indication, if approved.

Relevance of CHIT1 in pulmonary fibrosis and inflammation

While CHIT1 inhibition is not yet a clinically validated mechanism of action for the treatment of fibrotic and inflammatory diseases, Molecure has generated preclinical and animal model evidence of CHIT1's relevance in indications of this type. A key study demonstrated reduced fibrosis in a CHIT1 knockout (KO) mouse model of pulmonary fibrosis (Exhibit 4). In this, mice devoid of the gene for CHIT1 showed a significant reduction of pulmonary fibrosis (measured using the Ashcroft Fibrosis Score) when exposed to the chemotherapy drug bleomycin, which is intended to cause fibrotic lung injury. In addition, biomarkers for lung fibrosis were significantly and consistently reduced in the KO mice, indicating that CHIT1 activity is an important mediator in the development of fibrosis. We see these results as a meaningful genetic validation of CHIT1's importance in the development of fibrotic lung diseases and as encouraging support for the application of OATD-01 in this setting.

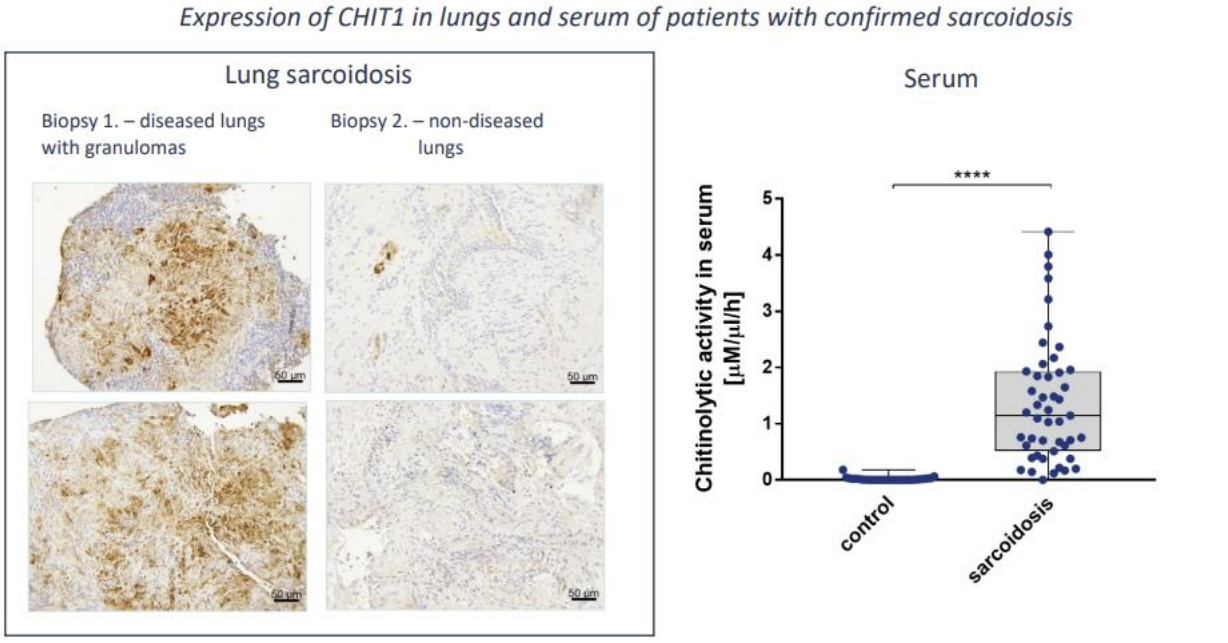
Exhibit 4: CHIT1 KO mouse model of pulmonary fibrosis



Source: Molecure corporate presentation

Molecure has also demonstrated that CHIT1 is highly expressed in the lungs of sarcoidosis patients, specifically in areas of lung biopsies affected by granulomas, and that chitinolytic activity in broncho-alveolar lavage fluid (BALF) and sputum is significantly enhanced (10–100x) in sarcoidosis and IPF patients (Exhibit 5). CHIT1 activity has also been shown to strongly correlate with the severity and progression of sarcoidosis and is therefore considered a reliable and sensitive biomarker of disease progression. We believe the combination of evidence presented above supports Molecure's pursuit of CHIT1 as a potential target for the treatment of sarcoidosis.

Exhibit 5: CHIT1 expression in sarcoidosis patients



Source: Molecure corporate presentation

Interstitial lung disease: Sarcoidosis and IPF

Sarcoidosis is a systemic inflammatory disease characterised by the presence of granuloma (clusters of immune cells), with severity ranging from mild to progressive and recurrent cases leading to lung fibrosis. The disease can affect almost any organ in the body, however over 90% of cases are located in the lungs. In general, sarcoidosis is a relatively rare disease. In the United States, the prevalence of sarcoidosis is estimated to be between 150,000 and 200,000 and the annual incidence rate is estimated at about eight cases per 100,000 people (Baughman, Field, Costabel, et al). However, the incidence and prevalence of the disease appears to be affected by several factors, including but not limited to race, region, age and sex. For example, in the United States, middle-aged (40–64 years old) non-Hispanic black women are consistently observed to have the highest sarcoidosis incidence and prevalence rates (238 per 100,000 average hospitalisation rate), with the mid-west United States having the highest regional rates. In contrast, estimated rates are consistently significantly lower in East Asia that other regions (incidence 0.5–1.3 per 100,000). In our view, these variable incidence and prevalence rates will be important for Molecure to understand when planning and executing clinical trials and commercial strategies.

Molecure believes OATD-01's mechanism of action may also be applicable to the treatment of 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. Symptoms include shortness of breath, a persistent dry cough and fatigue, and 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 (National Institutes of Health). Sarcoidosis and IPF are both classed as interstitial lung diseases and the similarities between serious cases of sarcoidosis (involving fibrosis) and IPF are clear.

Phase II proof-of-concept in sarcoidosis

In September 2020, Molecure announced the final results from a Phase Ib trial studying the safety and the pharmacodynamics of OATD-01 in healthy volunteers (n=24). The study used a multiple ascending dose design (25mg, 50mg), reporting good tolerability at each dose, no serious adverse

events and no adverse event that would lead to dose lowering or interruption over a 10-day course of treatment. At both 25mg and 50mg doses, pharmacodynamic analysis showed near total inhibition of CHIT1 plasma activity in enrolled volunteers, leading the company to abandon a planned 75mg dose.

With the global rights to OATD-01 now returned to the company, Molecure is planning to initiate a Phase II trial in sarcoidosis patients in Q2/Q323. Management has communicated that this will be a double-blind, randomised, placebo-controlled, multicentre, international study to assess the safety and efficacy of OATD-01 in first-line patients with active pulmonary sarcoidosis. We expect the trial to enrol c 60 patients over c 12 months and focus on endpoints such as reduction in inflammation, change in pulmonary function, time to improvement and migration from glucocorticoid use. We see the initiation of this Phase II trial as an important near-term catalyst for Molecure.

Standards of care present an opportunity

We believe that the clinical and preclinical data gathered by Molecure (and Galapagos) support OATD-01's development in sarcoidosis and potentially IPF. The commercial rationale for development in these indications is also compelling, in our view. For pulmonary sarcoidosis patients that require pharmacological intervention (up to 80% of cases spontaneously resolve), glucocorticoids (a class of immunosuppressive steroid hormone) represent the first-line therapy. The effect of glucocorticoids, with prednisone being the commonly used example, is the reduction of inflammation in the lungs. However, the long-term use of glucocorticoids is associated with serious side effects such as diabetes, osteoporosis, high blood pressure and Cushing's disease. If effects such as these limit the utility of glucocorticoids, other immunosuppressant drugs, such a methotrexate, may be administered. These drugs, however, come with their own safety concerns and long-term use is rarely appropriate. In IPF, the multiple tyrosine kinase (MTK) inhibitor nintedanib (Ofev, Boehringer Ingelheim) is often prescribed; it is associated with serious side effects such as gastrointestinal disorders, elevated liver enzymes, risks of bleeding and embryo-foetal toxicity. The only other drug approved for the treatment of IPF is pirfenidone (Esbriet, Roche), but this has its own toxicity issues and can cause elevated liver enzymes, gastrointestinal disorders and photosensitivity.

We note that both nintedanib and pirfenidone have been shown to reduce the rate of lung function decline (measured by forced vital capacity, FVC) by up to around 50%, but neither have been shown to reverse the fibrotic effect seen in IPF. Pirfenidone has been associated with improvement in all-cause mortality, whereas nintedanib has shown trends (but not reaching statistical significance) towards this. Given the generally limited efficacy and side effect profile of existing treatments for sarcoidosis and IPF, we see a significant unmet medical need in these indications and therefore an opportunity for OATD-01. This opportunity could be especially pronounced, in our opinion, if Molecure can demonstrate that OATD-01 has a disease-modifying effect and does not just slow the progression of fibrotic lung diseases.

Disease-modifying profile would maximise market impact

The sarcoidosis treatment market represents only a small portion of the total pulmonary fibrosis treatment market. For example, worldwide sarcoidosis treatment sales in 2026 are estimated to reach US$188m (EvaluatePharma), whereas the market for IPF drugs is expected to reach c US$3.2bn in 2026 after peaking at c US$5.7bn in 2024 (EvaluatePharma). Glucocorticoids and other immuno-suppressive drugs (ie the mainstays of sarcoidosis treatment) are inexpensive, hence the relatively small market size for sarcoidosis drugs. In our view, this presents two potential opportunities to Molecure. If OATD-01 continues to demonstrate the favourable safety profile seen in Phase Ib and can show a competitive anti-inflammatory effect in sarcoidosis, we believe it could represent a viable substitute for glucocorticoid use. We note the need for longer-term safety studies, which will be important in establishing OATD-01's potential to substitute chronic glucocorticoid use.

Additionally, should OATD-01 demonstrate a disease-modifying, anti-fibrotic modality in clinical trials, Molecure may be able command premium pricing, which management asserts could be c US$22,000 pa in sarcoidosis. The company estimates a value for the sarcoidosis market at maturity with a disease-modifying treatment could be over US$1.5bn. If a disease-modifying profile is established, we believe OATD-01 could be advanced in other fibrotic diseases and expect a large potential opportunity in the treatment of IPF.

Competitive landscape in fibrotic lung disease

As mentioned, the sarcoidosis treatment market is small and dominated by generic drugs that have serious potential side effects, whereas the IPF market is much larger, with Esbriet (2021 world-wide sales US$1.2bn) already generic and Ofev (2021 world-wide sales US$2.9bn) reaching a patent cliff in 2026. Exhibit 6 presents the development pipeline of competing drugs in sarcoidosis and IPF. As evidenced by the variety of mechanisms being investigated, it is clear, in our view, that the interest in exploring new, potentially disease-modifying pathways is high in the sector.

In sarcoidosis, we highlight the neuropilin-2 inhibitor efzofitimod, which is currently in a potentially registrational Phase III trial and has previously demonstrated dose dependant reductions in percent-predicted forced vital capacity (FVCPP) and corticosteroid use. As there are objectively fewer drugs being developed in the space (eg compared to IPF), we believe the barriers to entry in the sarcoidosis treatment market are relatively low, representing an opportunity for OATD-01 to garner market share, if approved. In contrast we expect future competition in the IPF market to be high, as after Ofev also comes off patent, the market is expected to fragment. However, considering the size of the IPF market we anticipate that, should OATD-01 demonstrate a reversal or considerable slowdown in the decline of FVC compared to Ofev or Esbriet, there is a reasonable opportunity for the drug to garner a moderate market share.

Exhibit 6: Section of the competitive landscape in sarcoidosis and IPF

Drug	Company	Status	Indication	Mechanism of action (administration)	Notes
Efzofitimod	aTyr Pharma	Phase III	Sarcoidosis	Neuropilin-2 inhibitor (intravenous)	Demonstrated a dose dependant reduction in FVCPP and reduction in corticosteroid use in randomised, placebo-controlled Phase Ib/IIa trial (NCT03824392). Potentially registrational, randomized, double-blind, placebo-controlled Phase III trial (NCT05415137, EFZO-FIT) initiated patient dosing in Q322. ODD in sarcoidosis granted in January 2022.
Namilumab	Kinevant	Phase II	Sarcoidosis	Anti-GM-CSF antibody (sub-cutaneous)	Randomized, double-blind, placebo-controlled RESOLVE-Lung Phase II trial (NCT05314517) initiated in April 2022. Expected completion January 2025. Primary endpoint mean change from baseline in FVCPP.
CMK-389 (NOV-8)	MorphoSys (Novartis)	Phase II	Sarcoidosis	IL-18-targeting antibody (sub-cutaneous)	Single-blinded, randomized, placebo-controlled Phase II trial (NCT04064242) initiated in August 2019, expected completion July 2023. Proof-of-concept trial in chronic pulmonary sarcoidosis.
Xeljanz	Pfizer	Phase I	Sarcoidosis	JAK1 inhibitor (oral)	In a Phase I pilot study (NCT03793439), Xeljanz allowed 60% of sarcoidosis patients (n=5) to successfully taper corticosteroids. Further investigator-led Phase I trial (NCT03910543) demonstrated average reduction of disease activity of 82.7% in 10 patients with cutaneous sarcoidosis.
RG6354	Roche	Phase III	IPF	Regulatory macrophage differentiation stimulant (intravenous)	Ongoing STARSCAPE Phase III trial (NCT04552899). Roche expects to launch in 2024. Demonstrated 48% reduction in FVC decline at 24 weeks in 117-patient Phase II trial.
TAS-115	Otsuka Holdings	Phase II	IPF	Mesenchymal epithelial transition inhibitor/vascular endothelial growth factor antagonist	In a Japanese Phase II trial 77% of IPF patients who completed 13-week administration showed attenuation of FVC decline. Development plan for North American or European markets unspecified
BI1015550	Boehringer Ingelheim	Phase III	IPF	Phosphodiesterase 4B inhibitor.	Randomised, double-blind, placebo-controlled, Phase II trial (NCT04419506) demonstrated median change in FVC in patients who were not on approved antifibrotics was +5.7mL vs -81.7mL for placebo over 12-week treatment period (n=147). Phase III (NCT05321069) in IPF initiated in September 2022.
Pamrevlumab (FG-2019)	FibroGen	Phase III	IPF	Connective tissue growth factor targeting antibody	In a Phase II trial (NCT01890265) Pamrevlumab reduced decline of FVCPP by 60.3% at week 48 (n=103). Two ongoing Phase III trials, NCT04419558 (Zephyrus II) and NCT03955146 (Zephyrus-I).

Source: EvaluatePharma, Edison Investment Research

In our view, Roche's Phase III STARCAPE trial (NCT04552899) of RG6354 in IPF, which is expected to report results in early 2023, represents an important near-term event in the IPF field. If RG6354 demonstrates a reversal of FVC decline, it may set the standard against which new anti-fibrosis drugs are measured, in our view. We also see BI1015550 (Boehringer Ingelheim), an oral PDE4B inhibitor, as an important comparator. The drug was granted breakthrough therapy designation by the FDA and showed an increase in FVC (at 12 weeks) in a recent Phase II study. A Phase III study is planned to start in H222. Finally, FibroGen's pamrevlumab (FG-2019) has also shown promising data in IPF. In a Phase II trial (n=103), the connective tissue growth factor targeting antibody reduced the rate of FVC decline by approximately 60% versus a placebo at 48 weeks. Data from the first Phase III study (Zephyrus-I) are expected in 2023.

OATD-02: Potential immunoncology asset

Molecure's second development programme is focused on dual ARG1/2 inhibitor OATD-02. The asset is currently completing the Polish regulatory process and the company expects OATD-02 will enter a Polish Phase I trial in Q422. Molecure intends to investigate OATD-02's use in oncology, where it believes ARG1/2 inhibition could help restore antitumour immune responses. ARG1/2 are arginine-depleting enzymes whose actions are associated with immunosuppressive tumour microenvironments (TME). Other ARG inhibitors, for example the Phase II asset numidargistat (Calithera Biosciences), are currently in clinical development, which we see as modest validation for ARG as a useful target in oncology.

Preclinical data have shown OATD-02 can effectively inhibit ARG1/2 and in animal models has demonstrated the ability to improve the efficacy of PD-(L)1 immune checkpoint inhibitors (ICIs) when administered in combination. We see OATD-02's preclinical evidence as validating the premise of advancing the drug to human trials. However, we note that preclinical and animal model data may not translate to a clinically meaningful effect in humans. We expect the company to pursue a similar development strategy with OATD-02 as it has with OATD-01, namely a regional Phase I trial followed by international Phase II trials, with the intention of signing a global development and commercialisation out-licensing deal if proof-of-concept is achieved in humans.

Phase I expected to begin in late-2022

Provided regulatory clearance is achieved, OATD-02 could enter Phase I studies in Q422, as communicated by management. We expect a trial of this type would primarily assess the safety and tolerability of OATD-02 as a monotherapy in solid-tumour patients with a secondary focus on response rates and survival. The clinical trial application (CTA) for Phase I was filed in August 2022 and management states the commencement of Phase I in Q422 could lead to top-line results in H224 (Exhibit 7). We expect that Molecure would initially conduct Phase I trials in Poland, before expanding to international sites in subsequent studies. If safety, efficacy and pharmacodynamic results are positive, we expect this would guide the design of a Phase I/II trial of OATD-02 in combination with ICIs in solid or potentially liquid tumours. We believe ICI combinations are an area where OATD-02 could have a significant impact, given preclinical data.

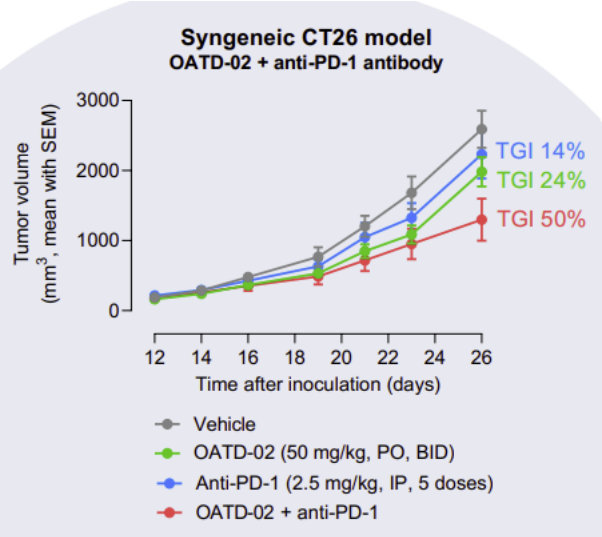
Exhibit 7: OATD-02 development timelines

Source: Molecure corporate presentation. Note: FPFV = first patient first visit, LPLV = last patient last visit, *CSR= clinical study report.

Preclinical data in oncology encouraging

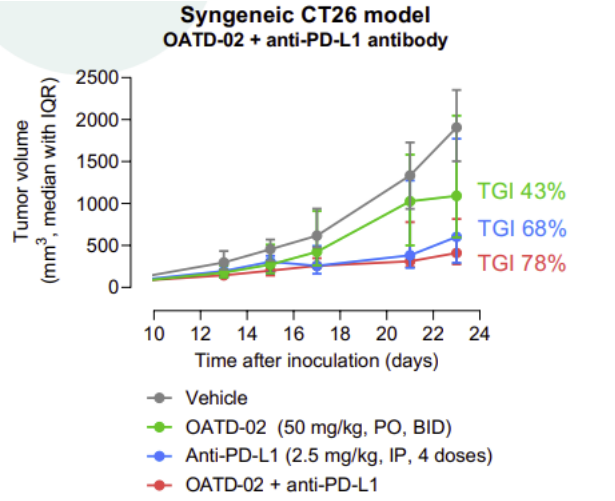
As with OATD-01, Molecure possesses a significant amount of preclinical data to support the clinical development of OATD-02 in oncology. For example, the company has demonstrated OATD-02's ability to restore the proliferation of ARG1 suppressed CD4+ and CD8+ T cells, an important component of the body's tumour immune response. In addition, OATD-02 has demonstrated dose-dependent reductions in tumour volume in mouse models of colorectal cancer as a monotherapy. Importantly, in our view, the drug has shown (in the same animal model) the capability to improve the efficacy of anti-PD-1 (Exhibit 8) and anti-PD-L1 (Exhibit 9) antibodies, when administered in combination. In our view, this collective data supports the development of OATD-02 in oncology indications as a monotherapy and confirms our opinion that a key commercial opportunity for the drug will be in combination with ICIs. We reiterate, however, that preclinical data may not translate into a meaningful clinical effect in humans. Results from the expected Phase I trial in solid tumours, expected in H224, could be a key catalyst in the OATD-02 development programme.

Exhibit 8: OATD-02 + anti-PD-1 anitbody animal model data



Source: Molecure corporate presentation. Note: TGI = tumour growth inhibition.

Exhibit 9: OATD-02 + anti-PD-L1 anitbody animal model data



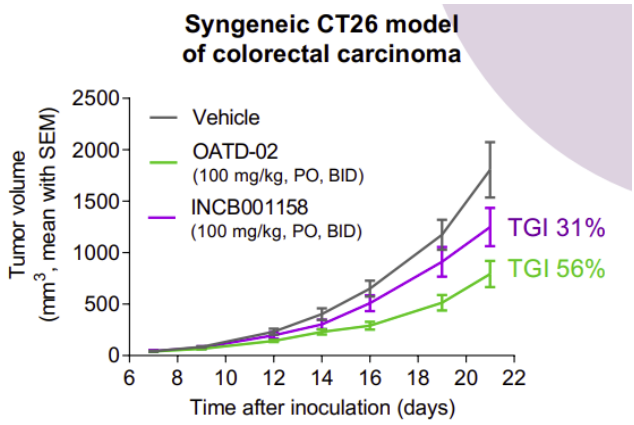
Source: Molecure corporate presentation. Note: TGI = tumour growth inhibition.

Competitive profile shown versus competition

In our view, a meaningful comparator, and potential competitor, for OATD-02 is the arginase inhibitor numidargistat (INCB001158), which is being developed by Calithera Biosciences and Incyte. As a Phase II asset, numidargistat represents the most clinically advanced arginase inhibitor being investigated in the oncology space, to our knowledge. The compound has demonstrated reasonable safety and tolerability in Phase I both alone and in combination with pembrolizumab (Keytruda, anti-PD-1 antibody, Merck) and is now in a Phase I/II trial (NCT02903914) to assess its efficacy in solid tumours.

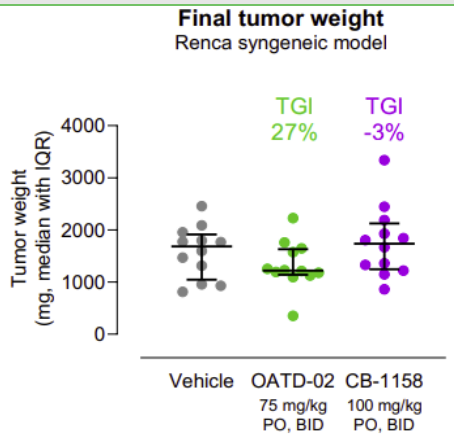
Molecure has conducted studies that suggest that OATD-02 monotherapy could have superior efficacy in solid tumours versus numidargistat. In mouse models of colorectal cancer (Exhibit 10), OATD-02 caused 56% tumour growth inhibition (TGI) compared to 31% for numidargistat when both were administered at a 100mg/kg dose. Additionally, in an ARG2 dependant mouse model of aggressive and low immunogenic renal cell carcinoma (RCC), OATD-02 demonstrated a 30% difference in TGI (27% vs -3% for numidargistat, Exhibit 11), based on final tumour weight. We caveat that comparison of OATD-02 to other potential competitors or arginase inhibitors based on these data is premature.

Exhibit 10: OATD-02 versus numidargistat in animal model of colorectal cancer



Source: Molecure corporate presentation

Exhibit 11: OATD-02 versus numidargistat in animal model of renal cell carcinoma



Source: Molecure corporate presentation

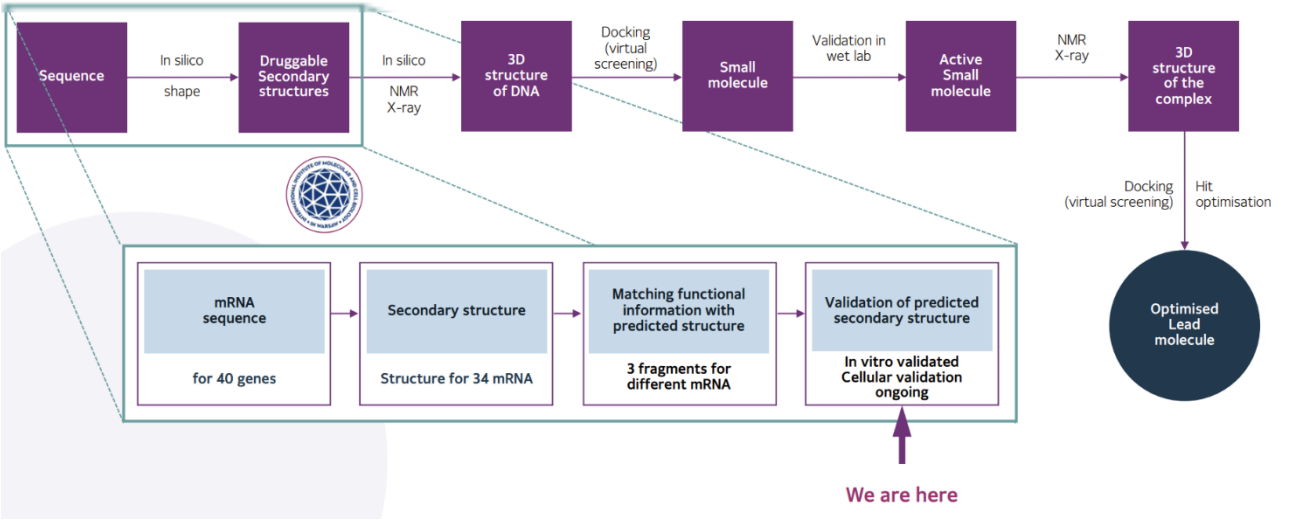
Company mission exemplified in discovery programmes

True to the company's mission to develop drugs that act on new targets, Molecure's preclinical pipeline and discovery platform contain a selection of innovative assets and technology, in our view. The company's USP7 programme is focused on the discovery of inhibitors of small molecules that inhibit ubiquitin specific protease-7 (USP7), an important enzyme in the regulation of cell homeostasis. Management expects that the lead asset in the programme, OAT-4828, will have confirmed in vivo efficacy in oncology by Q422, after which it could reach candidate nomination by Q323, with the intention of an IND submission by 2025. Molecure's other discovery programme is pursuing the discovery and development of YKL-40 binders in oncology indications. In addition, Molecure has a long-term licence option agreement with the University of Michigan to develop novel fibrosis-targeting compounds.

Further, the company is developing a technology platform focused on the discovery of small molecules that can bind to RNA and prevent downstream translation. The platform uses proprietary algorithms, developed by Professor Janusz Bujnicki, to predict the ability of small molecules to bind to RNA structures (predicted by a combination of algorithms and lab measurements). The identified molecules can then be synthesised and validated through biochemical and biophysical investigation. The company is currently in the process of validating its RNA druggable structure procedure (Exhibit 12) and expects in vitro proof of concept for the platform will be complete in Q223.

RNA-based platforms of this type can generate considerable value for companies that develop them, as demonstrated Amgen's research collaboration deal with Arrakis Therapeutics in January 2022. Arrakis has an RNA-targeting small molecule platform (that we believe is comparable to the one being developed by Molecure) and received an upfront payment of US$75m from Amgen for its use for five initial programmes, with potential milestone payments in future. For this reason, we see Molecure's RNA platform as a potential value driver for the company, if proof of concept is demonstrated. In particular, if the company can demonstrate improvements in speed or hit-quality over other platforms, potential partnering deals could be transformative.

Exhibit 12: Molecure's small molecule RNA-targeting platform



Source: Molecure corporate presentation

Sensitivities

As a pureplay biotech, Molecure is subject to all the regular sensitivities associated with drug research and development. The company's prospects may be affected by development delays or failures, regulator risks, competitor successes, partnering setbacks and financing risks. Molecure is focused on targeting new disease pathways with its drugs and, as such, OATD-01's and OATD-02's mechanisms of action have not yet been proven in a clinical setting. This, in our view, increases development risk for the company. Failure to demonstrate clinical proof of concept for OATD-01 in Phase II trials represents a significant near/medium-term risk and would likely cause the company to revaluate its long-term development timelines.

Molecure does not generate any revenues from its drug discovery and development operations. As the company advances through clinical trials, expenses are expected to significantly increase and, consequently, the company will require additional capital to fund its development objectives. Management's estimated cash runway will fund the company into Q224 and it will need to raise additional funds to complete OATD-01's Phase II trial. While Molecure is exploring non-dilutive funding option, capital could be raised through an equity offering, which could result in significant dilution of existing shareholders.

Financials

In the first nine months of FY22, Molecure reported revenues of PLN1.49m (US$0.31m), an increase from PLN0.87m in the first nine months of FY21, the majority of which is comprised of domestic research grants. Total operating costs up to end-Q323 increased to PLN9.00m from PLN6.09 in the same period a year prior (up to end-Q321) as the company continued to progress its pipeline and one-off costs from rebranding (previously OncoArendi) were recorded. Of this, PLN4.02m was attributed to external services and PLN3.82m to salaries, increased from PLN2.42m and PLN2.08, respectively, in the first nine months of FY22. Operating cash outflow up to end-Q322 was PLN6.50m and investing cash outflow stood at PLN21.3m, as the company capitalises parts of its R&D expenditure (PLN18.9m up to end-Q322). Molecure plans to be running two parallel clinical trials by end-FY23 (OATD-01 Phase II and OATD-02 Phase I), hence management expects cumulative expenditure over H222 and FY23 will increase dramatically to PLN58m (c US$11.6m). However, in the company's H122 earnings presentation, the USP7 programme was also listed as a

main cost driver over this period (along with OATD-01 and OATD-02), suggesting the company is preparing to ramp up preclinical work to progress this asset towards the clinic.

In FY21, Molecure reporting operating cash outflow of PLN13.5m (versus operating cash inflow of PLN57.4m in FY20) and investing cash outflow of PLN18.8m, which included PLN16.4m in capitalised R&D costs. In FY20 the company reported PLN124.9m revenue, due largely to the US$28m payment from Galapagos for the rights of OATD-01.

At end-September 2022, the company reported a cash position of PLN80.7m (US$16.9m), from PLN102.0m at end-FY21, reflecting PLN21.2m in total cash outflows in the year to date. Accounting for the increased future cash burn, management expects current resources to sufficiently fund the company's operations to Q224 (18–20 months). Management is also exploring potential sources of non-dilutive funding through various mechanisms. For example, the company's agreement with the University of Michigan resulted in a submission to the National Institutes of Health (NIH) in the United States for a potential c US$2m grant. The company is also intending to submit another NIH grant application (c US$2m) for OATD-01 in late 2022. Other funding options being considered by management include other R&D grants and collaborative agreements (cost/profit sharing, milestones). In total, the company estimates that these sources could potentially fund 30–50% of costs. Furthermore, if the company can demonstrate the utility of its RNA platform, we see this as a potential source of future revenues, through licensing deals or usage agreements.

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