Atriva Therapeutics

(Currently listing via BioCure Technology, CSE: CURE)

Share Price: C$0.015

Next generation influenza antiviral developer

Atriva Therapeutics is a privately held host-cell targeting antiviral drug developer based in Munich which is currently going public on the Canadian Securities Exchange via a reverse take-over of BioCure Technology (CSE: CURE). Atriva's lead candidate is zapnometinib, a small molecule which has been studied in Phase 2 in patients hospitalised with severe Covid-19 and which will enter a Phase 2 clinical development program in 2024 in severe influenza. Atriva has raised more than EUR40m in capital since its 2015 founding, with backing from venture capital, the European Investment Bank, and the German government.

A drug that worked in Covid-19

Zapnometinib, also known as ATR-002, is an orally available small-molecule inhibitor of MEK1/MEK2 with immunomodulatory and antiviral properties. The drug was discovered around 2015 by scientists at the University of Tubingen in Germany. A Phase 2 study of zapnometinib in severe SARS-CoV-2 infection had to be cut short because of the emergence of the Omicron virus variant and a lack of severely diseased patients in late 2021 but found a trend towards significance in terms of a reduction in clinical severity status at day 15 versus placebo. The drug has an excellent safety profile and, importantly, since it does not target the virus directly, but the host-cells required by RNA viruses for replication and simultaneously responsible for immune response regulation, it does not cause drug-resistance.

A valuable opportunity in influenza

There are approved direct-acting antivirals for the early phase of influenza, but they typically need to be administered within the first 48 hours. Moreover, the virus can build up resistance to these drugs by mutating the surface proteins that these drugs target. Zapnometinib would represent a better alternative in severely diseased patients, positioning Atriva to benefit from a regular seasonal influenza market valued in the billions, as well as for pandemic preparedness and necessary stockpiling.

Currently raising US$15m

Atriva is currently raising US$15m to progress zapnometinib into Phase 2 in severe influenza. The key risks that we see for Atriva are (1) delays in initiating the Phase 2a human viral challenge study; (2) clinical risk; and (3) funding challenges.

CSE: CURE, OTCQB: BICTF

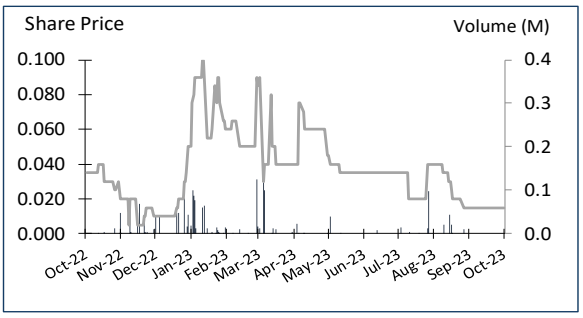
Sector: Healthcare

20 November 2023

Market Cap. (C$ m)	1.2
# shares outstanding (m)	99.9
# shares fully diluted (m)	108.0
Market Cap Ful. Dil. (C$ m)	1.3
Free Float	0.7
52-week high/low (C$)	0.075 / 0.015
Avg. 12M daily volume ('1000)	3,400.0
Website	www.biocuretech.com

Source: Company, Pitt Street Research

Share price (C$) and avg. daily volume (k, r.h.s.)



Source: Refinitiv Eikon, Pitt Street Research

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Disclosure: Pitt Street Research directors own shares in Biocure Technology.

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Introducing Atriva Therapeutics

Who is Atriva Therapeutics? Atriva Therapeutics (atriva-therapeutics.com) is a privately held drug developer based in Munich. The company is focused on host-cell-targeting antiviral and immunomodulatory therapies. Atriva's lead candidate is zapnometinib, an orally available small molecule which has been studied in Phase 2 in patients hospitalised with a severe SARS-CoV-2 infection (Covid-19). Atriva is now preparing zapnometinib for clinical studies in patients hospitalised with a severe influenza infection. Atriva has raised more than EUR40m in capital since its 2015 founding, with backing from venture capital, the European Investment Bank[1], and the German government. Atriva announced in September 2023 that it was planning to go public on the Canadian Securities Exchange via a reverse take-over of BioCure Technology Inc. (CSE: CURE) to fund further the development of zapnometinib in influenza.

What is zapnometinib, Atriva's lead candidate? Zapnometinib, also known as ATR-002, is an orally available small-molecule inhibitor of MEK1/MEK2 with immunomodulatory and antiviral properties. The drug was discovered around 2015 by scientists at the University of Tubingen in Germany.

Zapnometinib noticeably reduced the severity of Covid-19 infection in Phase 2 in some patients.

What is the evidence that zapnometinib is an effective antiviral? A Phase 2 study of zapnometinib in severe Covid-19, which had to be cut short because of the emergence of the Omicron virus variant and a lack of severely diseased/hospitalised patients in late 2021. However, the study found a trend towards significance in terms of a reduction in clinical severity status at day 15 versus placebo.

Why is zapnometinib's next study going to be in influenza? There are approved antivirals, the so called direct-acting antivirals, for the treatment of the early phase of influenza but they typically need to be administered within the first 48 hours after patient experiences symptoms. Moreover, the influenza virus can build up resistance to these drugs by mutating the surface proteins that these drugs target. Atriva's drug interferes with virus replication inside host cells, which would avoid this resistance issue, and rebalance an overshooting immune response at the same time.

Beyond influenza, what is in Atriva's pipeline? The company believes that zapnometinib and other candidates in Atriva's portfolio can be useful against other RNA viruses such as hantavirus, Respiratory Syncytial Virus (RSV) and Dengue fever. In January 2022 the FDA granted zapnometinib Orphan Drug designation for the treatment of hantavirus infections.

What is the current transaction that will take Atriva public? Atriva announced in September 2023 that it would be doing a reverse takeover (RTO) of Biocure Technologies (CSE: CURE), a company traded on the Canadian Securities Exchange. In this transaction the shareholders of Atriva will receive not less than 75% of the securities of the resulting issuer. Prior to completion of the RTO in late 4th quarter of 2023, Atriva intends to raise US$15m in new capital.

What is the timeline for the influenza clinical work? The company hopes to commence its Phase 2 development program in severe influenza in the second half of 2024:

- First will be a challenge study in healthy volunteers, where those volunteers are infected with a live attenuated version of an influenza virus and then treated with zapnometinib to demonstrate the drug's antiviral activity and immunomodulatory capacity.

[1] The lending arm of the European Union.

- After this challenge study will come the Phase 2b trial in patients hospitalised with a severe influenza infection. This study can straddle both hemispheres to recruit patients wherever influenza infections are rising.

Ten reasons to look at Atriva Therapeutics

1. **Zapnometinib is potentially the Next Big Thing in influenza antivirals**, since it does not prompt drug resistance, is synergistic with direct acting antivirals, and has immunomodulatory capacity.
2. **Zapnometinib's ability to blunt a cytokine storm (i.e., an overshooting immune response) is new in influenza treatment**. Deaths caused by severe influenza are usually related to cytokine storms. The evidence from the clinic as well as *in vivo* that zapnometinib can blunt expression of pro-inflammatory cytokines in Covid is therefore encouraging.
3. **Zapnometinib performed well in Covid-19**, with a Phase 2 in severely diseased/hospitalised patients reporting a trend towards significance in terms of a reduction in clinical severity status at day 15 versus placebo.
4. **Zapnometinib could return to the clinic soon**, with a human viral challenge trial to demonstrate the drug's antiviral and immunomodulatory activity in healthy individuals infected with influenza as early as in mid-2024 (subject to funding availability).
5. **Influenza is a significant market opportunity**. The total annual global market just for direct-acting influenza antivirals is probably US$1.5bn, if sales of oseltamivir and zanamivir in the mid-2010s are any guide[2].
6. **Atriva benefits from pandemic preparedness efforts globally**. The Covid-19 pandemic of 2020-2022 has public policy makers concerned about how healthcare systems can be ready for the Next Pandemic, which may be an influenza pandemic [3]. Consequently, drug development programmes like Atriva's may attract more public funding, and the drug itself may be a candidate to be stockpiled.
7. **Zapnometinib has multiple potential indications beyond influenza**, with the drug likely to be useful against other RNA viruses such as Respiratory Syncytial Virus (RSV) and Dengue fever.

Atriva has raised >EUR40m to date.

8. **Atriva has been through some serious due diligence since 2015,** thanks to the >EUR40m in capital raised to date. The company has obtained validation and backing from venture capital, the European Investment Bank, and the German government.
9. **Atriva has secured Orphan Drug status for zapnometinib**, with the drug being granted it by the FDA for hantavirus in January 2022. Infection with a hantavirus, one of several viruses that are carried by rodents, is rare[4], but the Orphan Drug status can assist in market exclusivity and the ease of clinical entry.
10. **Atriva has solid management**, with CEO Christian Pangratz, a long-time veteran of the Life Sciences scene, having gained valuable experience at Nektar Therapeutics in the US and at

[2] For background see tsrlinc.com/market-potential.
[3] Exp Mol Med. 2021 May;53(5):737-749. Epub 2021 May 6.
[4] Int J Surg Open. 2022 Dec; 49: 100582. Published online 2022 Nov 24.

Vectura/Skyepharma in Europe. Backing Pangratz is a notable board chaired by Dr Ulrich Dauer, the German biotechnology entrepreneur which includes Professor Stephan Ludwig, the scientific founder who first identified the potential of the compound which became zapnometinib.

Zapnometinib as a next-generation host-cell-targeting antiviral drug for influenza

Atriva Therapeutics was founded to develop a better way to treat influenza[5]. The company has its origins in the work of Professor Stephan Ludwig, now head of the Institute of Virology at the University of Muenster in Germany. Ludwig had noticed that many of the cell signalling pathways that are activated in cancer cells are also activated in host cells used by the influenza virus for replication. He hypothesised that drugs blocking such pathways would therefore indirectly act against influenza infections. A breakthrough came when he used a Pfizer drug candidate called CI-1040[6] to block a pathway called MAPK and was able to show marked reduction of ability of influenza to replicate inside host cells. Ludwig and his fellow virologist Dr Stephan Pleschka filed for patent protection over this host-cell-targeting approach[7] and the work was published in the journal *Nature Cell Biology* in 2001[8]. CI-1040 is a MEK inhibitor. Pfizer dropped this compound after a Phase 2 failure in 2003[9], so it was available for repurposing in 2015 when Ludwig and Pleschka, with immunologist Dr Oliver Planz of the University of Tubingen, cofounded Atriva Therapeutics to develop the idea of MEK inhibition in host cells[10]. *In vivo*, CI-1040 metabolises into its acidic form, ATR-002, and Atriva found that this compound was much more effective in terms of better absorption and potency *in vivo* compared to the mother compound. Consequently ATR-002, now called zapnometinib, was the drug over which Atriva filed intellectual property[11]. Before Atriva could study zapnometinib in influenza in humans, the Covid-19 Pandemic arrived in 2020, providing a different, albeit somewhat unexpected, RNA virus infection to clinically test the drug against.

Influenza can be deadly in a bad season - 284,000 may have died globally in 2009.

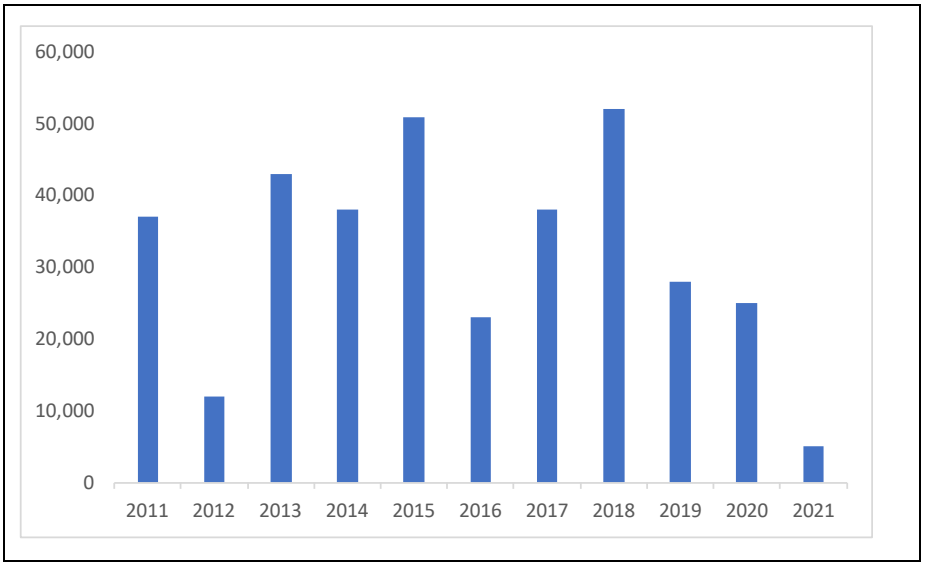
What is influenza? Influenza is a highly infectious viral illness caused by the influenza virus, an RNA virus. Influenza tends to be much more severe than the common cold, featuring symptoms such as rapid onset of fever, muscle aches, joint pain, headache, sore throat, and cough. Generally, it lasts up to ten days but is sometimes followed by a secondary illness such as pneumonia. Influenza is seasonal in that it tends to show up in the colder months. The strain of influenza in circulation varies from season to season, which is why every season's vaccine is different[12]. Many cases, albeit not enough, can be prevented by immunisation, but sometimes the disease becomes so severe it can kill. Some seasons are particularly bad in terms of the mortality - in the 20th Century there were influenza pandemics in 1918 (the big one[13]), 1957[14],

[5] For background see Nat Med. 2017; 23(5): 528–531.
[6] For background on CI-1040 see Semin Oncol. 2003 Oct;30(5 Suppl 16):105-16.
[7] See WO/2001/076570, priority date 7 April 2000.
[8] Pleschka et. al. (2001), *Influenza virus propagation is impaired by inhibition of the Raf/MEK/ERK signalling cascade*. Nat Cell Biol. 2001 Mar;3(3):301-5.
[9] Molecules. 2017 Oct; 22(10): 1551. Published online 2017 Sep 26.
[10] Ludwig, Pleschka and Planz remain on Atriva's Scientific Advisory Board.
[11] WO/2020/212478, *Novel MEK inhibitor for the treatment of viral and bacterial infections*. Invented by Oliver Planz, priority date 16 April 2019.
[12] Influenza strains are denoted by the letters H and N, referring to two structures in the virus, hemagglutinin, and neuraminidase. There are 18 different H subtypes and 11 different N subtypes. H1N1 is the 'swine flu' strain which generated a human pandemic in 2009. 1918 was caused by H1N1, 1957 was H2N2, and 1968 was H3N2.
[13] 20-40% of the worldwide population became ill and more than 50 million people died.
[14] This Asian flu pandemic probably killed 1.1 million people globally. See J Infect Dis. 2016 Mar 1; 213(5): 738–745. Published online 2016 Apr 4.

and 1968[15]. Two types of influenza, called 'A' and 'B', cause outbreaks in people. Both types can cause mild to severe illness in all age groups but while influenza A viruses infect humans and other animals, influenza B viruses affects only humans.

Influenza remains an area of high unmet medical need, despite new drugs. Since 1999-2000 there have been effective direct-acting antivirals against both A and B[16] to treat the early phase of the disease. However, people are still dying from severe (later stage) influenza infections. Between 2011 and 2020 the US alone recorded an average of 35,000 'influenza-associated' deaths[17] . The global figure has been estimated at close to 400,000 deaths a year[18]. Vaccines reduce the incidence of severe infections but not completely, with seasonal efficacy generally less than 60% and can sometimes be as low as 10%[19]. Therefore, antiviral therapies against severe influenza will remains a staple of managing the disease and healthcare cost burden of influenza, especially for high-risk patients (children, the elderly, and immune-suppressed patients). Also, severe influenza caused by more pathogenic strains, such as, for example, H1N1, the 'swine flu' strain from 2009 caused and will continue to cause epidemics if not pandemics. It is estimated that swine flu caused 284,000 deaths globally[20], and since 1997 the cross-species spread of avian influenza viruses[21] has become increasingly frequent.

Figure 1: Estimated US influenza-related deaths, 2011-2021



Source: CDC

[15] This Hong Kong flu pandemic is estimated to have caused between 500,000 and two million deaths worldwide – see ERJ Open Res. 2016 Jan; 2(1): 00013-2016. Published online 2016 Mar 11.
[16] A drug called amantadine was first approved by FDA as a prophylactic agent against Asian influenza in 1966 and against influenza A in 1976, however until the development of oseltamivir and zanamivir nothing much seemed to work against the trickier influenza B. Amantadine today is mostly used to treat dyskinesia associated with parkinsonism.
[17] Seasonal influenza may lead to death from other causes, such as pneumonia, heart failure, or Chronic Obstructive Pulmonary Disease. Only counting deaths where influenza was recorded on a death certificate grossly underestimates influenza's true impact.
[18] J Glob Health. 2019 Dec; 9(2): 020421.
[19] CDC, Seasonal Influenza Vaccine Effectiveness, 2005-2015.
[20] Cureus. 2018 Jan; 10(1). Published online 2018 Jan 9.
[21] Such as H5N1, H7N9, and H10N8.

There are currently four FDA-approved direct-acting antiviral drugs used in influenza:

- **Oseltamivir**, which gained FDA approval in October 1999 after earlier development by Roche and Gilead Sciences. The companies have been marketing the drug as Tamiflu ever since and it went generic in 2016.
- **Zanamivir**, which gained FDA approval in April 2000 and was marketed as Relenza by GlaxoSmithKline. This drug was originally developed by a Melbourne-based company called Biota[22]. It was, unfortunately, a commercial failure because Tamiflu is orally available, whereas Relenza was delivered by inhalation, using a puffer called a 'Diskhaler'.
- **Rapivab**[23], generic name peramivir, for which BioCryst Pharmaceuticals[24] gained FDA approval in December 2014.
- **Xofluza**[25], generic name baloxavir marboxil. This drug, which was discovered by Shionogi & Co. of Japan, gained FDA approval in October 2018. It is marketed by Shionogi and Roche.

Influenza antivirals in 2009 represented a US$3bn market.

Sales of direct-acting antiviral drugs for influenza vary with the severity of the season but the market is large. Roche made US$709.5m from Tamiflu in 2015, a mild flu year, but in 2009, during that year's H1N1 swine flu outbreak, sales skyrocketed to US$3.2bn.

The existing direct-acting antiviral drugs are effective but primarily in mild or early-stage disease and can also lead to drug resistance. Take Xofluza as a good example. In the Phase 3 'Capstone-1' study the median time to alleviation of symptoms was about 54 hours whereas with placebo it was 80 hours. Oseltamivir worked at about the same speed although baloxavir was faster at lowering viral load on the first day[26].

- The first three of the abovementioned drugs – oseltamivir, zanamivir and Rapivab – are neuraminidase inhibitors. Neuraminidase is an enzyme which studs the surface of the influenza virus. When the virus invades a cell, it starts to use that cell's replication machinery to churn out new copies of itself. The resulting new viruses are initially bound to the outside of the infected cell, until neuraminidase breaks these bonds, setting the new viruses free to go looking for other cells to infect.
- The fourth drug, Xofluza, inhibits cap-dependent endonuclease in the polymerase acidic protein. This is a subunit of the viral polymerase, the enzyme responsible for influenza virus replication. The different target represented an improvement over the neuraminidase inhibitors because baloxavir interferes with the ability of the flu virus to multiply, while the older drugs merely interfere with the ability of the flu virus to spread within the body.

The trouble with all these drugs – the neuraminidase inhibitors as much as Xofluza – is that, in addition to the slowness with which they work, they can lead to the development of drug resistant variants because they target the virus directly. The swine flu outbreak was caused in part by strains of H1N1 that had become resistant to oseltamivir[27]. For Xofluza, the Capstone-1

[22] Back in the late 1970s and early 1980s it started to occur to the ANU's Graeme Laver, the CSIRO's Peter Colman, and other Australian scientists, that it was possible to create a drug which blocked this enzyme, and that that drug could go on to be a huge breakthrough in the treatment of influenza. The hitherto untreatable B virus was as much reliant on neuraminidase for its ability to spread as type A. Block neuraminidase, the Australian influenza visionaries hypothesised, and one limits the ability of both A and B viruses to spread. It took years to realise this vision of a neuraminidase inhibitor drug, but in 1989 Biota was able to announce that, using some sophisticated rational drug design techniques, it had developed just such a compound. For background see Colman et. al. (1987), *The three-dimensional structure of a complex of antibody with influenza virus neuraminidase*. Nature, 326: 358-363.

[23] See rapivab.com.

[24] Durham, NC, Nasdaq: BCRX, biocryst.com.

[25] See xofluza.com.

[26] N Engl J Med. 2018 Sep 6;379(10):913-923.

[27] Drugs. 2009;69(18):2523-31.

investigators noted the emergence of 'reduced susceptibility' to the drug because of variants in close to 10% of recipients.

Zapnometinib is arguably a superior drug because it combines two positive effects in case of infection – it targets host cell factors that are required for influenza virus propagation, without having to act on the virus itself, and it interferes with the overshooting immune system during infection. Zapnometinib, as a MEK inhibitor, blocks the Raf/MEK/ERK kinase pathway, one of the more important of the MAPK pathways and, as we suggested above, vital to influenza viral replication. Cells divide and proliferate through various cellular signalling cascades where one protein acts on another. This network of proteins is called a 'pathway', and they are vital to healthy cellular functioning. However, when the influenza virus enters a host cell, it can hijack such pathways for its own ends. The Raf/MEK/ERK pathway, for example, is used by the influenza virus to export its so-called ribonucleoprotein complexes – basically, influenza particle works-in-progress – out of the nucleus of the infected cell. Zapnometinib as a MEK inhibitor can block the activation of that pathway, so levels of the virus coming out of each infected cell go way down. Importantly, the actual structure of the virus isn't touched by zapnometinib, because the MEK pathway is induced or upregulated by the virus. Furthermore, the downregulation of the pathway reduces the intensity of the immune response without completely shutting it down, thereby reducing the severity of diseases which is normally driven by the overshooting immune response.

Zapnometinib is potentially the Next Big Thing in influenza antivirals, for four main reasons:

Unlike today's influenza antivirals, Zapnometinib does not prompt drug resistance.

- It does not prompt drug resistance, meaning that it can potentially be a 'broad spectrum' treatment independent of virus strains.
- The safety of the drug is excellent, so patients tolerate treatment very well.
- The drug has demonstrated synergistic treatment effect with direct acting antiviral in *in vitro* and *in vivo* experiments[28].
- The drug also possesses an immunomodulatory capacity. Atriva found this when it looked for example at the drug *in vivo* in Covid-19 and found that the expression of pro-inflammatory cytokines – which could be so deadly in that infection – had been reduced[29].

A Phase 2 study in severe Covid-19 provided evidence that zapnometinib was an effective host-cell-targeting antiviral. A Phase 1 study had established zapnometinib's safety profile in 2019[30]. Not long after that, Covid-19 arrived. The pandemic presented an opportunity to try out this novel compound, given that Covid-19, like influenza, is an RNA virus and interferes with the Raf/MEK/ERK kinase pathway. Atriva's Phase 2 RESPIRE study of zapnometinib in severe Covid-19, which was initiated in mid-2021[31], was meant to recruit 220 patients but was cut short by the emergence of the Omicron variant in late 2021, which stalled recruitment due to a lack of severely diseased and hospitalised Covid-19 patients. In the end there were 101 patients evaluated, almost equally split between zapnometinib and placebo. The primary endpoint was a reduction in Clinical Severity Score at day 15 after treatment initiation - treatment with zapnometinib or placebo

[28] See Hamza et. al. (2021), *Improved in vitro efficacy of Baloxavir Marboxil against Influenza a virus infection by combination treatment with the MEK Inhibitor ATR-002.* Front Microbiol . 2021 Feb 12:12:611958.
[29] Schreiber et. al. (2022), *The MEK1/2-inhibitor ATR-002 efficiently blocks SARS-CoV-2 propagation and alleviates pro-inflammatory cytokine/chemokine responses*. Cell Mol Life Sci. 2022 Jan 10;79(1):65.
[30] See NCT04385420 at clinicaltrials.gov.
[31] See NCT04776044 at clinicaltrials.gov.

was for six days. This study, on the reduced numbers, missed statistical significance in the primary endpoint, however predefined subgroup analyses identified strong trends for improved Clinical Severity Scores in patients with severe disease at baseline (p=0.13) and non-Omicron variants (p=0.10). The study results were reported by Atriva in September 2022 and were published in eClinicalMedicine (part of THE LANCET Discovery Science) in October 2023[32].

Atriva wants to start the first clinical studies of zapnometinib in 2024.

The first studies in influenza are coming. Atriva is currently working on launching a Phase 2 development program in influenza. This would involve two studies with zapnometinib. First, a human viral challenge trial to demonstrate the drug's antiviral and immunomodulatory activity in healthy individuals infected with an attenuated influenza virus strain. The challenge study will be followed by a Phase 2 clinical trial in patients hospitalised with a severe influenza infection to show zapnometinib's safety and efficacy in a larger population of potentially up to 500 patients. The company believes it can have the drug ready for the human viral challenge trial as early as second quarter of 2024.

Influenza antivirals are an important public health tool. We noted above that some influenza seasons can be severe. The recent Covid-19 pandemic has meant that governments are now more focused on pandemic preparedness in general, and that will likely mean stockpiling of influenza antivirals. We believe that can benefit emerging drug developers like Atriva. This stockpiling is, arguably, a market opportunity in the billions.

Atriva's pipeline

Zapnometinib is, potentially, a 'pipeline in a product', because it will likely have utility in a range of RNA virus infections. As we noted above, Atriva is considering the drug's use in hantavirus, Respiratory Syncytial Virus (RSV) and Dengue fever.

Hantavirus. Hantavirus is a relatively new virus that was only identified in 1978. The virus, which is carried by rats and mice, causes hemorrhagic fevers, Acute Respiratory Distress Syndrome (ARDS), and renal failure[33]. The virus only showed up in the United States in 1993 in the so-called Four Corners region shared by Arizona, New Mexico, Colorado, and Utah. It remains rare, accounting for only 20 or 30 cases a year in the US[34] but often makes the news because of the fatalities that it causes, since around one in three people who are infected will die from it[35]. Hantavirus is of public policy interest because of its potential to be weaponised for bioterrorism[36]. Consequently, Atriva's pre-clinical evidence of the utility of zapnometinib in hantavirus, and the Orphan Drug designation granted by the FDA in January 2022, has potential to attract government funding and possibly military funding. While this indication is non-core for Atriva at present it could yield significant shareholder value in the future [37]. We note, for example, that Siga Technologies [38] has built a significant pipeline around biodefense and a

[32] Rohde et. al., *Efficacy and safety of zapnometinib in hospitalised adult patients with COVID-19 (RESPIRE): a randomised, double-blind, placebo-controlled, multicentre, proof-of-concept, phase 2 trial*, The Lancet eClinicalMedicine, 4 October 2023.
[33] The virus got its name from the Hantan River in South Korea, near which around 3,000 cases of hemorrhagic fever were reported among UN troops during the Korean War.
[34] Emerg Infect Dis. 2013 Dec; 19(12): 1934–1937.
[35] See, for example, *Mother and son in Arizona die from rat-borne virus that kills one in three patients who catch it* by Luke Andrews, The Daily Mail, 16 July 2023.
[36] Front Bioeng Biotechnol. 2020; 8: 925. Published online 2020 Aug 7.
[37] WO/2021/069486, *MEK inhibitors for the treatment of hantavirus infections*, Invented by Oliver Planz, priority date 8 October 2019.
[38] New York, NY, Nasdaq: SIGA, siga.com

market capitalisation in the hundreds of millions based in part on a smallpox treatment.

Respiratory Syncytial Virus (RSV) [39]. RSV is a virus that causes acute respiratory infection in individuals of all age groups but can be severe in infants, impacting some 1-3% of children under 12 months of age in the United States are hospitalised as a result. AstraZeneca's Synagis, generic name palivizumab, which was one of the first approved monoclonal antibody drugs, gained FDA approval in 1998 for the prevention of RSV. It blocks the virus's ability to enter host cells and was a commercial success because of the routine administration of the drug to infants. A new monoclonal called Beyfortus, generic name nirsevimab, from Sanofi and AstraZeneca, gained FDA approval in July 2023. Nirsevimab is a big step forward from palivizumab because it has a higher potency and more than three times the half-life, so a single infusion can last for an entire RSV season. Synagis sales peaked in 2013 at just under $1.5bn per year. Nirsevimab could potentially double that[40]. Zapnometinib's potential in this new market is that monoclonal antibody drugs are often expensive and must be delivered via infusion. Zapnometinib as an orally available small molecule would likely be a lower cost option that is easier to deliver.

Currently there are no approved drugs for Dengue fever

Dengue fever. Dengue fever, caused by the mosquito-borne dengue virus, is characterised by the flu-like symptoms fever, headache, and joint pain, however in more severe cases, though, blood vessels can become damaged by the virus, leading to dengue haemorrhagic fever. It's estimated that around 100 million cases a year, mostly in the world's temperate zones, can lead to 40,000 deaths[41]. Dengue has started to show up in less temperate parts of the world as the global climate warms up and is therefore of more interest to pharm companies than traditionally[42]. Since 2015 there has been a vaccine marketed by Sanofi called Dengvaxia, but that vaccine is only about 60% effective[43]. There are no drug treatments, but there is at least US$300m global market for any new Dengue drugs that can be developed[44].

Atriva has solid leadership

CEO Christian Pangratz, who joined Atriva in January 2023, brings more than 25 years of senior experience in Life Sciences. At Nektar Therapeutics[45], where he worked from 2004 to 2011, Pangratz served as Executive Director Business Development, closing one of the company's largest and strategically most significant business transactions. After his return to Europe, he was Executive Vice President of Business Development, Alliance Management and Project Management at the respiratory drug delivery company Skyepharma until that company's merger with Vectura. Pangratz joined Vectura after the merger[46] and helped the company get a joint venture further established in China. At Sterna Biologicals, an immunotherapy company focused on inflammation, Pangratz oversaw early clinical studies and helped keep the company funded.

[39] The virus is 'syncytial' because of the large cells known as syncytia that form when infected cells fuse.
[40] See *Sanofi, AZ's blockbuster hopeful RSV med nears first approval as showdown with Pfizer, GSK looms* by Fraiser Kansteiner, Fierce Pharma, 16 September 2022.
[41] Zeng et. al. (2021), *Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017*. EClinicalMedicine. 2021 Jan 6:32:100712.
[42] Front Public Health. 2022 May 27:10:884645.
[43] N Engl J Med. 2015 Sep 24;373(13):1195-206.
[44] Antiviral Res. 2012 Nov;96(2):203-12.
[45] San Francisco, Ca., Nasdaq: NKTR, mektar.com.
[46] Bought by Philip Morris International in 2021.

The Atriva Therapeutics board is Chaired by the German bioentrepreneur **Dr Ulrich Dauer,** most noted for his leadership of Vivoryon Therapeutics[47], which developed varoglutamstat in Alzheimer's. Its other members are **Professor Stephan Ludwig** of the University of Muenster, who has guided the science behind zapnometinib from the get-go; **Michael Grissinger**, an American pharma industry veteran who has done business development at J&J, Ciba-Geigy, SmithKline Beckman, and Upjohn; **Dr Piet Wigerinck**, former Chief Scientific Officer of Dutch biotech company Gallapagos; and **Paul Lelieveld,** a Dutch specialist in life sciences commercialisation now with Meneldor, a seed and early-stage life sciences venture fund.

Appendix I - Papers relevant to Atriva Therapeutics

Laure et. al. (2020), *Antiviral efficacy against influenza virus and pharmacokinetic analysis of a novel MEK-inhibitor, ATR-002, in cell culture and in the mouse model.* Antiviral Res. 2020 Jun:178:104806. Epub 2020 Apr 15.

- This paper compares the antiviral potency and bioavailability of Pfizer's old CI-1040 compound versus its major active metabolite ATR-002, *in vitro* as well as in the mouse model. It established that ATR-002 was the more effective candidate.

Hamza et. al. (2021), *Improved* in vitro *efficacy of baloxavir marboxil against Influenza a virus infection by combination treatment with the MEK Inhibitor ATR-002*. Front Microbiol . 2021 Feb 12:12:611958.

- This paper reports that zapnometinib is synergistic with Xofluva *in vivo*.

Schreiber et. al. (2022), *The MEK1/2-inhibitor ATR-002 efficiently blocks SARS-CoV-2 propagation and alleviates pro-inflammatory cytokine/chemokine responses*. Cell Mol Life Sci. 2022 Jan 10;79(1):65.

- This paper shows *in vivo* that zapnometinib can blunt the sometimes-severe cytokine storms associated with Covid-19 infection.

Koch-Heier et. (2022), *Pharmacokinetics, pharmacodynamics, and antiviral efficacy of the MEK inhibitor zapnometinib in animal models and in humans.* Front Pharmacol. 2022 Jun 15:13:893635.

- This paper shows *in vivo* that zapnometinib can work at low doses.

Schreiber et. al. (2022), *The MEK1/2 inhibitor ATR-002 (zapnometinib) synergistically potentiates the antiviral effect of direct-acting anti-SARS-CoV-2 drugs.* Pharmaceutics. 2022 Aug 25;14(9):1776.

- This paper reports that zapnometinib is synergistic with known Covid-19 antivirals such as Gilead's Remdesivir, the drug which gained FDA approval for use in hospitalised Covid-19 patients in October 2020.

Full et. al. (2022), *Pharmacokinetics, absorption, distribution, metabolism, and excretion of the MEK inhibitor zapnometinib in rats*. Front Pharmacol. 2022; 13: 1050193, published online 2022 Dec 5.

- This paper showed the favourable ADME profile of zapnometinib.

Schussele et. al. (2022), *Establishment of a novel method to assess MEK1/2 inhibition in PBMCs for clinical drug development*. Front Cell Dev Biol. 2022 Dec 12:10:1063692.

- This paper covers a new assay involving a dye called propidium monoazide (PMA) to show that zapnometinib works by MEK inhibition.

[47] Munich, Germany, Euronext Amsterdam: VVY, vivoryon.com.

Ludwig et. al. (2023), *MEK inhibition with zapnometinib as a treatment for RNA virus infections: The dual benefit of host immunomodulation and antiviral activity*. Curr Opin Virol. 2023 Apr; 59: 101304, published online 2023 Feb 24.

- This paper shows that drugs like Atriva's work because if the immunomodulatory ability as well as the ability to inhibit viral replication.

Appendix II - Atriva's Intellectual property

Atriva Therapeutics owns various published patent families with broad international coverage related to the use of MEK inhibitors and other kinase inhibitors for antiviral therapies. For zapnometinib the relevant patent family is WO/2020/212478, where the composition-of-matter patent life runs to 2041.

WO/2001/076570, *Use of substances that act as cascade inhibitors of the RAF/MEK/ERK signal cascade, for producing a medicament to treat DNA and RNA viruses.* Invented by Stephan Ludwig and Stephan Pleschka, priority date 7 April 2000.

- This method-of-use patent application covers the original MEK inhibition approach developed by Ludwig and Pleschka around 2001.

WO/2014/056894, *MEK inhibitors in the treatment of virus diseases*. Invented by Stephan Pleschka, Oliver Planz and Stephan Ludwig, priority date 8 October 2012.

- This second method-of-use patent application updates the original MEK inhibition.

WO/2015/173788, *Novel anti-infective strategy against influenza virus and* S. aureus *coinfections*. Invented by Christina Ehrhardt and Stephan Ludwig, priority date 16 May 2014.

- This patent application covers the use of MEK inhibition to treat bacterial infections associated with the original influenza infection.

WO/2017/050717, *Substance for prophylaxis and treatment of infections by influenza viruses*. Invented by Oliver Planz, Carmen Hartmayer, Sascha Rohn and Peer Riehle, priority date 21 September 2015.

- This patent application covers the potential for influenza prophylaxis, much as current antiviral drugs are sometimes used prophylactically.

WO2019/076947, *Novel MEK inhibitor for the treatment of viral and bacterial infections.* Invented by Stephan Ludwig and Oliver Planz, priority date 17 October 2017.

- This patent application covers ATR-002 (PD0184264), the active metabolite of CI-1040, as Atriva's MEK inhibitor.

WO/2020/188034, *RSK inhibitors in the treatment of virus diseases*. Invented by Stephan Ludwig and Oliver Planz, priority date 19 March 2019

- This patent application covers inhibitors of RSK, a downstream target of the Raf/MEK/ERK pathway which Atriva identified in 2020 could be important in virus-induced export of viral ribonucleoproteins[48].

WO/2020/212478, *Novel MEK inhibitor for the treatment of viral and bacterial infections.* Invented by Oliver Planz, priority date 16 April 2019.

- This patent application covers ATR-002 (PD0184264), the active metabolite of CI-1040, as Atriva's MEK inhibitor.

[48] Schreiber et al. (2020), *Dissecting the mechanism of signaling-triggered nuclear export of newly synthesised influenza virus ribonucleoprotein complexes*. PNAS, June 2020.

WO/2021/037956, *Combinations of MEK inhibitors with cap-dependent endonuclease inhibitors.* Invented by Oliver Planz and Hazem Ewess, priority date 27 August 2019.

- This patent application covers the combination of zapnometinib with drugs like Xofluza.

WO/2021/069486, *MEK inhibitors for the treatment of hantavirus infections*, Invented by Oliver Planz, priority date 8 October 2019.

- This patent application covers the use of zapnometinib in hantavirus.

WO/2021/214200, *ROCK inhibitors for use in treating or preventing pulmonary edema*. Invented by Irina Kuznetsova, Susanne Herold, John Ziebuhr, Stephan Pleschka and Christin Peteranderl, priority 22 April 2020.

- This patent application covers inhibitors to Rho-kinase, a protein that may be involved in the vascular dysfunction associated with Covid-19 infection.

WO/2021/234097, *MEK inhibitors for the treatment or prevention of coronavirus infections and/or Covid-19 cytokine storm*. Invented by Stephan Ludwig, Oliver Planz, Helen Elisa Hoffmann, Julia Koch-Heier and Michael Schindler, priority date 20 May 2020.

- This patent application covers the use of zapnometinib in Covid-19.

WO/2023/094556, *MEK inhibitors for the prevention and treatment of Long Covid syndrome.* Invented by Oliver Planz and Yvonne Full, priority date 24 November 2021.

- This patent application covers potential Long Covid applications of zapnometinib, relevant because of the immunomodulatory capabilities of the compound, which can reasonably reduce the tissue damage causative of Long Covid.

Appendix III - Comparable companies to Atriva Therapeutics

Cidara Therapeutics Inc (Nasdaq: CDTX). This company's Cloudbreak platform allows the development of 'drug-Fc conjugates' that couple small molecules and peptides to human antibody fragments for better targeting. Cidara's CD388 product, which targets viral neuraminidase, is being developed in collaboration with J&J's Janssen unit and recently generated promising interim efficacy and safety data from the Phase 2a study evaluating pre-exposure prophylaxis.

Cocrystal Pharma (Nasdaq: COCP). This antiviral drug developer is working on drug candidates that target the replication process of coronaviruses (including SARS-CoV-2), influenza, norovirus, and Hepatitis C. The lead candidate, CC-42344, completed Phase 1 in late 2022. A Phase 2a human challenge study in the UK is planned.

Poolbeg Pharma (LSE: POLB). This company's POLB 001 drug is designed to blunt the severe inflammation associated with influenza infection. A Phase 1 human challenge trial with lipopolysaccharide, known to be highly immunogenic, showed marked reduction in cytokines as well as various markers of systemic and local inflammation. POLB 001, by avoiding targeting the virus itself and by leaving necessary immune functions intact to fight the infection, is, in effect, strain agnostic,

Veru Pharma (Nasdaq: VERU). This company's Sabizabulin drug is a microtubule disruptor, meaning that it can bust up the intracellular transport

structures vital to RNA viruses Sabizabulin has enjoyed Phase 3 success in moderate-to-severe Covid-19[49] and is now in a confirmatory study. The drug is currently being studied in hospitalised Influenza patients at high risk for ARDS.

Vir Biotechnology (Nasdaq: VIR). This company's platforms allow new antibody and T Cell-based drugs to be discovered. The company is currently in the clinic with a range of candidates targeting Hepatitis B, influenza A and B and Covid-19, among others. VIR-2482 recently completed Phase 2 in influenza and showed disease reductions at the highest dose.

Appendix IV - Glossary

Acute Respiratory Distress Syndrome (ARDS) – The rapid build-up of fluid in the air sacs in the lungs, preventing oxygen to reach the bloodstream.

ADME – See Pharmacokinetics.

Composition-of-matter – A claim in intellectual property law over the chemical composition of a new drug.

COVID-19 – An infectious disease caused by the SARS-CoV-2 virus.

Dengue virus – The virus that causes Dengue fever, a disease characterised not only by fever but also rashes, headaches, and muscle pain.

Endpoint – The outcome or outcomes that a clinical trial is designed to evaluate, such as disease progression or death. Generally clinical trials have primary and secondary endpoints.

Hantavirus – One of several viruses that are carried by rodents. Hantavirus infection is characterised by pulmonary edema, hypoxia, and hypotension.

Immunomodulatory – Either augmenting or suppressing an immune response.

Influenza – A disease mainly of the upper respiratory tract caused by the influenza virus and characterised by high fever and severe malaise, among other things. Two types of influenza, called 'A' and 'B', cause outbreaks in people.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Kinase – An enzyme that phosphorylates, or adds a phosphate group onto, other molecules to turn them 'on' or 'off'. Kinases are often cancer drug targets.

Live attenuated – A virus that has been weakened so that it can used foe vaccination purposes of as a challenge virus to test an antiviral drug.

MEK – A kinase in the Raf/MEK/ERK pathway targeted by zapnometinib.

Orphan Drug – A drug that benefits less than 200,000 potential patients in the US. Orphan drug designation provides tax benefits as well as market exclusivity.

Pharmacokinetics – The study of the time course of a drug's absorption, distribution, metabolism, and excretion from the body.

Respiratory Syncytial Virus (RSV) – A common respiratory virus that usually causes mild, cold-like symptoms. Infants are more likely to develop severe RSV and need hospitalisation.

[49] Barnette et. al. (2022), *Oral Sabizabulin for High-Risk, Hospitalized Adults with Covid-19: Interim Analysis*. NEJM Evid 2022;1(9), published July 6, 2022.

RNA – A nucleic acid 'photocopier', used in copying each individual strand of DNA for use in making proteins (messenger RNA) and in delivering amino acids to the ribosome for assembling into a protein (transfer RNA).

RNA virus – A virus with RNA rather than DNA as the genetic material. Influenza is an RNA virus.

Virus – A strip of DNA or RNA surrounded by a protein coat that is capable of replication only within human or animal cells. Influenza is a virus as are Hepatitis C, Dengue and SARS.

Zapnometinib – An orally available small-molecule inhibitor of MEK1/MEK2 useful in treating influenza infection.

Appendix V - Risks related to Atriva Therapeutics

Risks specific to Atriva. We see five major risks for Atriva Therapeutics as a company and as a (potentially) listed stock:

- **Timing risk.** There is the risk that zapnometinib may take longer than expected to move through the clinic.
- **Regulatory risk**. There is the risk that regulators may decline to approve Atriva's products, even if the company considers the data submitted to be adequate.
- **Commercial risk**. There is the risk that Atriva may fail to find commercial partners for its products, given the unusual market dynamics of antivirals.
- **Uptake risk**. There is the risk that Atriva's products are still too expensive in the healthcare markets in which it wants to participate.
- **Funding risk**. There is the risk of future capital raisings proving dilutive to existing shareholders.

Risks related to pre-revenue Life Science companies in general.

The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.

Since most biotechnology and medical device companies listed on stocks exchanges in Canada and around the world fit this description, the 'term' speculative can reasonably be applied to the entire sector.

The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Atriva.

Appendix VI – Analyst Qualifications

Stuart Roberts, lead analyst on this report, has been an equities analyst since 2002.

– Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
– Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research speciality at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies, such as CSL, Cochlear and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
– After 15 months over 2015–2016 doing Investor Relations for two ASX-listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Sciences companies.
– In July 2016, with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Sciences companies.
– Since 2018, Stuart has led Pitt Street Research's Resources Sector franchise, spearheading research on both mining and energy companies.

Nick Sundich, lead analyst on this report, is an equities research analyst at Pitt Street Research.

- Nick obtained a Bachelor of Commerce/Bachelor of Arts from the University of Sydney in 2018. He has also completed the CFA Investment Foundations program.
- He joined Pitt Street Research in January 2022. Previously he worked for over three years as a financial journalist at Stockhead.
- While at university, he worked for a handful of corporate advisory firms.

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