PITT STREET RESEARCH

Island Pharmaceuticals

A company-defining 12 months lie ahead

Share Price: A$0.19

Island Pharmaceuticals (ASX: ILA) is an ASX-listed biotech company developing its flagship drug ISLA-101 against mosquito diseases. After years of research and successful clinical data, the company has commenced a Phase II study of ISLA-101 for Dengue fever. Results from the first cohort are expected prior to Christmas 2024, with full results in 2025.

ASX: ILA

Sector: Healthcare

15 October 2024

Market cap. (A$ m)	33.6
# shares outstanding (m)[1]	176.9
# shares fully diluted (m) [1]	265.4
Market cap ful. dil. (A$ m)	50.4
Free float	100%
52-week high/low (A$)	0.19 / 0.053
Avg. 12M daily volume ('1000)	183.8
Website	www.islandpharmaceuticals.com

Source: Company, Pitt Street Research

[1] After first tranche of placement on 11 October 2024

ISLA-101

ISLA-101 (or fenretinide) is a drug that is being repurposed for the prevention and treatment of dengue fever and other mosquito-borne viruses (flaviviruses). ISLA-101 prevents the nuclear entry of a particular viral protein from entering the host cell-nucleus and hijacking it. Prior to its repurposing, ISLA-101 was tested for other indications too in dozens of clinical trials in cancer and respiratory illnesses and these all showed the drug's safety. Preclinical work at Monash University uncovered ISLA-101's potential as an anti-viral drug and the research ILA has undertaken to date against Dengue fever (as well as Zika) has been unanimously positive.

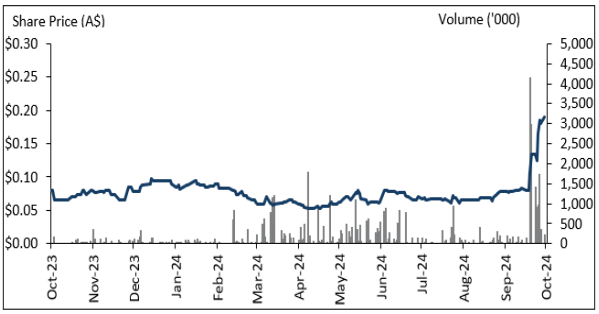
The diseases Island Pharmaceuticals is targeting are major problems for societies

Flaviviruses generally are a major societal problem. Dengue alone is endemic in over 100 countries and infects 400 million people annually. There are no treatments for the fever, only symptomatic relief medicines like paracetamol or mosquito repellents like sprays and nets. Moreover, the spread flaviviruses are expected to intensify in the future because of climate change and increasing urbanisation. The biodefence agent galidesivir that Island is currently evaluating (outlined in Appendix I), could represent a new treatment for Ebola and Marburg virus infections.

Valuation range of A$0.31-$0.41 per share

After a $3.5m placement in October 2024 we value ILA at A$83m in a base case scenario and A$109.1m in an optimistic (or bull) case scenario – equating to $0.31 per share and $0.41 per share respectively under the current number of shares on issue. Although ILA share price has until recently suffered due to a delay in the commencement of the Phase II trial, we see ILA being re-rated if the trial is successful. A failure of the trial is the key risk facing this stock. Please see p.24 for further risks associated with an investment in ILA.

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



Source: Refinitiv Eikon, Pitt Street Research

Valuation metrics	
NPV fair valuation range (A$)	0.31-0.41
WACC	15.5%

Source: Pitt Street Research

Analysts: Stuart Roberts, Nick Sundich

Tel: +61 (0)4 3483 8134

Stuart.Roberts@pittstreetresearch.com

Nick.Sundich@pittstreetresearch.com

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Introducing Island Pharmaceuticals (ASX: ILA)

Island Pharmaceuticals (ASX: ILA) is a biotech company focused on repurposing drugs for viral infections.

Island Pharmaceuticals (ASX: ILA) is a biotech company focused on repurposing drugs for viral infections. Island's flagship asset is ISLA-101 (fenretinide), and the company is about to commence a Phase II trial of ISLA-101 against Dengue fever called PROTECT, which stands for PROphylactic and TrEatment Challenge Trial. The PROTECT trial follows several years of pre-clinical research of this compound against flaviviruses, unanimously depicting the drug's potential efficacy. This is the first clinical investigation of fenretinide against any flavivirus. There are years of clinical research with this compound in other indications demonstrating its safety.

11 key reasons to look at Island Pharmaceuticals

1) **A major 12 months lies ahead of the company**. The Biotech Bear Market of 2022-23 has resulted in several biotech stocks being sold off, particularly those that have been perceived to either not be advancing or with milestones too far away. Nonetheless, this has not stopped certain biotechs that have achieved clinical milestones from creating shareholder value. Island Pharmaceuticals has a major 12 months ahead during which the company is expected complete PROTECT (its Phase 2 trial), which will be the most comprehensive study conducted of ISLA-101 in mosquito diseases. Successful data could be the catalyst for a re-rating of the company in and of itself, as well as other value-creating catalysts including progression to Phase 3 and potential licensing or commercial deals.
2) **Island carries less risk than other pharmaceutical companies** for several reasons. These reasons all stem from the fact that ISLA-101 is a repurposed drug with a substantial history of safety data. Repurposed drugs take less time, cost less to bring through the clinic, and carry less risk of clinical trial failure compared to – albeit without eliminating that risk entirely.
3) **If successful against Dengue fever, ISLA-101 could be quickly adapted to other flaviviruses (like West Nile, Zika and yellow fever).** This is because the Mechanism of Action is the same and the aforementioned viruses spread throughout the body in the same way. The process of regulatory approval against further flaviviruses could be faster than would otherwise be the case. This would open up an even more significant commercial opportunity than the opportunity of Dengue fever only – although of course, the market for Dengue fever is appetising in its own right.
4) **The company's key partnerships that have and continue to enable the company to progress ISLA-101**. Island's key partnership has been with Monash University, which outlicensed ISLA-101 to the company continues to collaborate to this day. This partnership has been a key to the company reaching the current phase of development and will be going forward. Also of note is ILA's agreement with the US Army under a CRADA (Cooperative Research and Development Agreement) allowing the company to use a US Army developed virus in the trial. It is also providing funding, in conjunction with the State University of New York.
5) **Dengue fever, and flaviviruses generally, are a problem and ISLA-101 offers a solution**. Dengue fever alone impacts over 400m people annually and causes a wide range of symptoms such as aches, pains, fevers. Moreover, the problem of mosquitos is expected to get worse due to climate change, which has potential to be a boom for mosquito

populations, providing ideal conditions for them to breed and thrive. There is also the potential risk of flaviviruses such as Dengue being used as bioweapons. There is an urgent need for new solutions for these epidemics.

6) **ILA can have a market all to itself**. This is because there are no treatments for dengue fever when it hits. There are only a handful of vaccines that (despite efficacy) are not appropriate to use in all patients, and treatments for certain symptoms of dengue fever. ISLA-101 would be able to grab a significant share of the potential market if it were to prove itself as the first drug that could fight dengue fever.
7) **Less time and money will be sacrificed than would ordinarily be the case with a clinical trial**. Clinical trials can be long in duration and costly to companies, but this will not be the case. Island is a beneficiary of a US$625k grant to conduct the trial[1], leaving the remaining cost at US$1.1m. Moreover, the company expects to receive a full set of data in the next 6 months, because of the short incubation period of Dengue, which will allow them to move quickly through the trial. These will reduce the risks of shareholder dilution in the short to medium term, although there will likely need to be further capital raised for a Phase 3 trial unless outlicensed.
8) **Island could obtain a Priority Review Voucher at the time of approval**. This will mean that in addition to the standard regulatory approval, ILA will be permitted to expedite the approval process for another drug or sell it to another company. PRVs can sell for over US$100m – as judged by the ten most recent PRVs. It goes without saying that such a non-dilutive cash injection would be spectacular for the company.
9) **Island's management team**. Island Pharmaceuticals has a highly capable management team with extensive experience in managing publicly listed biotech companies and creating shareholder value. In particular, Executive Chair Paul MacLeman previously served as Managing Director and/or CEO of several VC funded, ASX, NASDAQ, CSE and TSX listed companies. We also note the board has ownership in the game with >15% ownership in the business.
10) **Island Pharmaceuticals is potentially a player in biodefense**, with its signature in September 2024 of binding Letter of Intent with BioCryst for an antiviral molecule called galidesivir, that has been shown to have a broad spectrum of activity in viruses including Ebola, Marburg, yellow fever and Zika, as well as MERS and SARS-CoV-2. For more on this see Appendix I.
11) **We believe ISLA-101 is substantially undervalued**. The company's market capitalisation (currently around <$30m) is more appropriate for a company at a pre-clinical stage, rather than at a company conducting a Phase II clinical trial. We think the company is significant undervalued, a factor due to the long delay in commencing the Phase 2 trial. The results of that trial will be the key catalyst for the company's future. A successful trial could lead to a re-rating of the company towards levels more fitting of a later-stage clinical trial company. We have valued the company at A$83.0m (or $0.31 per share) in a base case scenario and A$109.1m (or $0.41 per share) in our bull case.

[1] The grant actually went to SUNY but Island is the beneficiary of the funds because they are being used for its study.

The Background of Island Pharmaceuticals (ASX: ILA)

Island Pharmaceuticals was founded in 2020 and listed on the ASX in May 2021.

Island Pharmaceuticals was founded in 2020 and listed on the ASX in May 2021 but traces its origins back to 2017. In that year a company called Isla Pharmaceuticals was incorporated by American biotech entrepreneurs William Garner and David Foster. Upon Island's ASX listing, Isla US became a wholly owned subsidiary of the ASX-listed company and Isla's shareholders became shareholders in the new company.

The intention of the company when it listed was to take its flagship asset ISLA-101 to a Phase II clinical trial for Dengue Fever, an objective it is set to realise before the end of 2024.

Island's strategy of drug repurposing explained

At the time Island listed, the company attracted attention from investors as one of the few ASX companies with a focus on flaviruses. The company's advisory board, which included Professor Stephen Thomas (the lead principal investigator for the Pfizer/BioNTech's COVID-19 vaccine trial), arguably helped too. But it is also one of the few companies that is repurposing a drug.

Drug repurposing involves using a drug that has been tested for other indications for a new indication for which it has not previously been tested for.

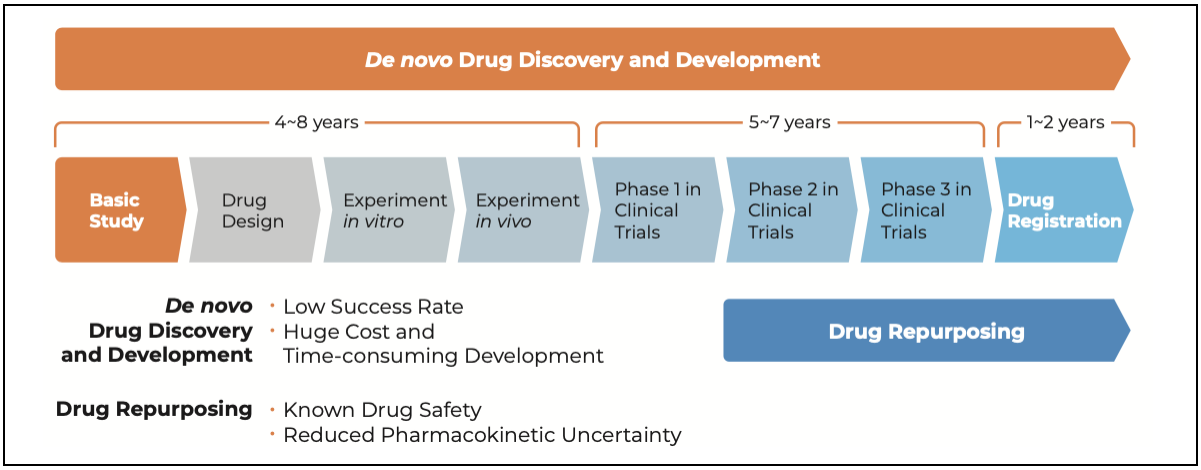
Most clinical stage biotechs are starting from scratch with a drug that has not been tested in other indications, but drug repurposing involves using a drug that has been tested for other indications for a new indication for which it has not previously been tested for. In certain instances, the specific drug may have been received regulatory approval and been commercialised for other indications. In other instances, it may have failed to pass clinical trials for efficacy – although of course, such drugs would have had to have passed for safety.

Examples of successfully repurposed drugs include:

- **Aspirin** which was initially market as an analgesic in 1899, but repositioned in the 1980s as an antiplatelet aggregation drug that could prevent cardiovascular events. This was due to the work of British pharmacologist John Vane, a discovery that won him a Nobel Prize in 1982.
- **Sildenafil/Viagra** which is now a treatment for erectile dysfunction, but was initially investigated by Pfizer in 1985 as a treatment for angina (a type of chest pain caused by reduced blood flow to the heart), but repurposed before coming to market as its effect on erections was noticed as an unexpected side effects during clinical trials. Many may not know that Pfizer continued with this original research and in 2005 obtained approval for pulmonary hypertension, under the brand name Revatio.
- **Dimethyl fumarate** which was first synthesised in 1819 as an anti-fungal agent but gradually came under scrutiny for causing allergies, leading to the EU banning the manufacturing of products with more than 0.1ppm of dimethyl fumarate in 1998 and the importation of such products in 2009. Nonetheless, it has been used in Germany since the 1990s to treat psoriasis. It was repurposed by Biogen to treat multiple sclerosis (MS) and was a gamechanger because it could be taken orally, and even with the risk of allergies, is still less cardiotoxic than other drugs that were used at the time.

When drugs are repurposed, the time and cost to bring it to market are significantly reduced because certain earlier stages (i.e. pre-clinical and Phase 1) can sometimes be by-passed (Figure 1).

Figure 1: The advantages of repurposing a drug



Source: Company

A typical drug bought to market from discovery could cost US$2.87bn and take up to 15 years. But one estimate suggests a repurposed drug could take 6.5 years and cost US$300m.

It is estimated that the typical drug successfully bought to market from discovery could cost US$2.87bn and take up to 15 years[2]. There are varying estimates of how long it takes a repurposed drug to get to market, but practically *all* estimates are lower. One estimate is 6.5 years and US$300m in costs[3][4]. Some particular drugs cost and take even less to get to market. For instance, Propranolol took 4 years (from a commencement of a Phase III study in February 2010 and regulatory approval in March 2014) to be repurposed for severe infantile haemangiomas (IHs) and was estimated to have cost US$18.9m[5].

Drug repurposing does come with certain challenges including the risk that the drug may not work for the indication or that there may be patent protection preventing the drugs' repurposing. The latter is less relevant to ISLA-101 because the only patent protection has been that which Island Pharmaceuticals itself has secured. The former is still a risk, although the risk is somewhat lower now that the company is about to commence a Phase 2 trial, and the data to date has unanimously suggested that the drug is efficacious against flaviviruses, and that it is safe for human consumption.

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10097740/
[3] Ibid
[4] This estimate assumed such drugs would have to undergo both Phase II and Phase III clinical trials prior to approval.
[5] Persidis A. The benefits of drug repositioning. *Drug Discov World.* 2011;12:9–12

The journey of ISLA-101 pre-listing

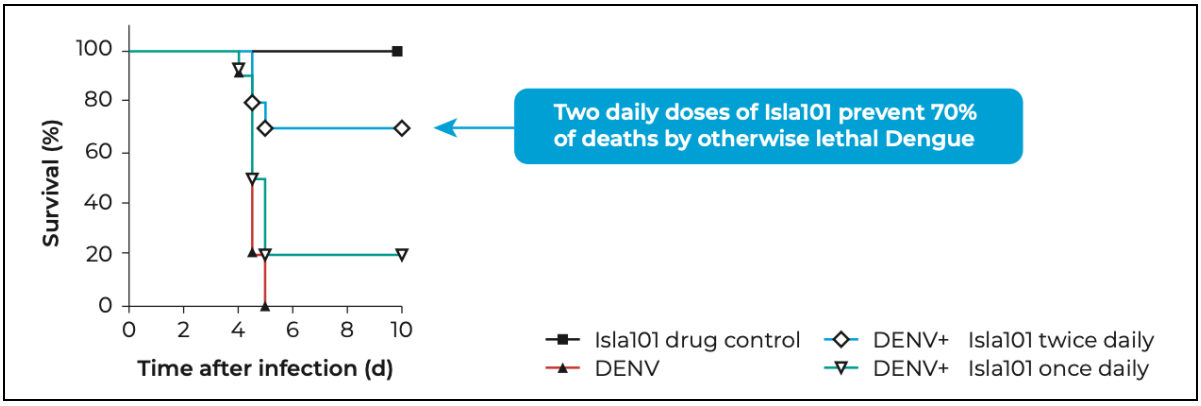
Island Pharmaceuticals' ISLA-101 (or ferentinide), had been the subject of ~45 Phase I and II human clinical trials as a therapeutic for cancers and various respiratory illnesses, given its chemo-preventative properties. Although the drug was proven safe, it was not efficacious in these indications, and its development was abandoned by Johnson & Johnson. The program was donated to the US National Cancer Institute (NCI).

ISLA-101 has activity against all four strains of dengue, as well as Zika virus, West Nile virus, Yellow Fever and chikungunya virus.

Monash University picked up the drug and conducted pre-clinical research that showed it has potential as an efficacious anti-viral drug. Island licensed it in from Monash University, retaining a research partnership with it. ISLA-101 had been identified by Monash from a library of small molecules that demonstrated activity in screens for molecules that prevented cells being infected by the dengue virus. Research completed to data have shown that ISLA-101 has activity against all four strains of dengue, as well as Zika virus, West Nile virus, Yellow Fever and chikungunya virus (Figures 2 and 3).

In in-vitro models, ISLA-101 has shown broad anti-viral activity as well as anti dengue-1 activity in in-vitro models using fresh human cells. In animal models, ISLA-101 was shown to be protective in dengue fever and Zika. In extremely lethal animal models, ISLA-101 was shown to prevent death in 70% of subjects[6].

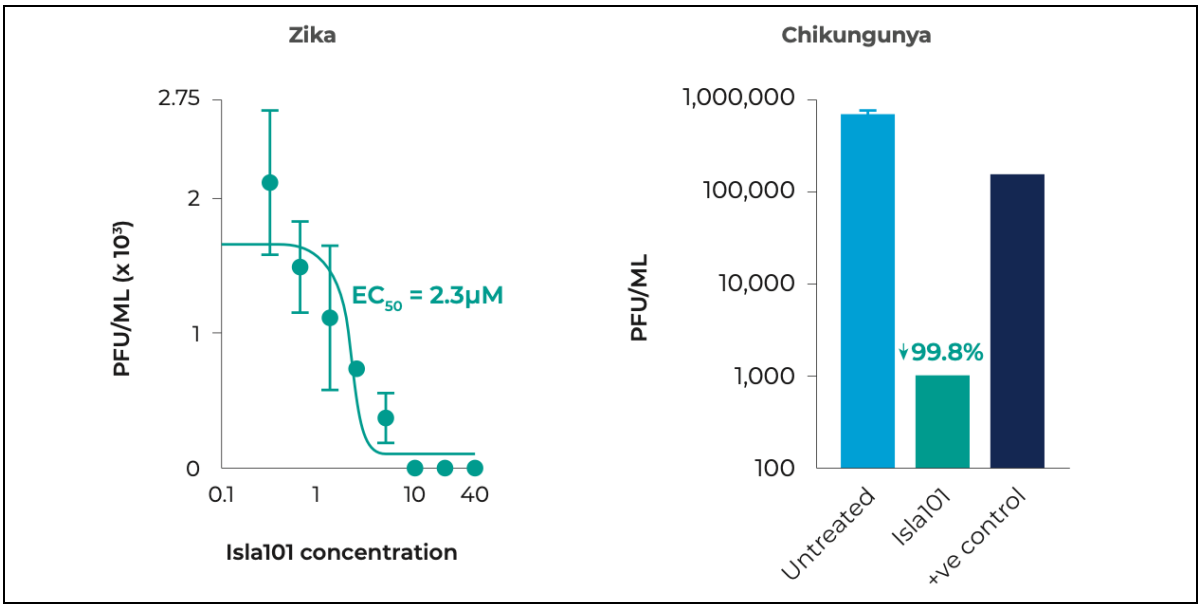
Figure 2: ISLA-101's efficacy against Dengue



Source: J Infect Dis. 2014 Dec 1;210(11):1780-91. Epub 2014 Jun 5.

[6] Dengue rarely kills human patients, making this animal study particularly severe.

Figure 3: ISLA-101's efficacy against other flaviviruses



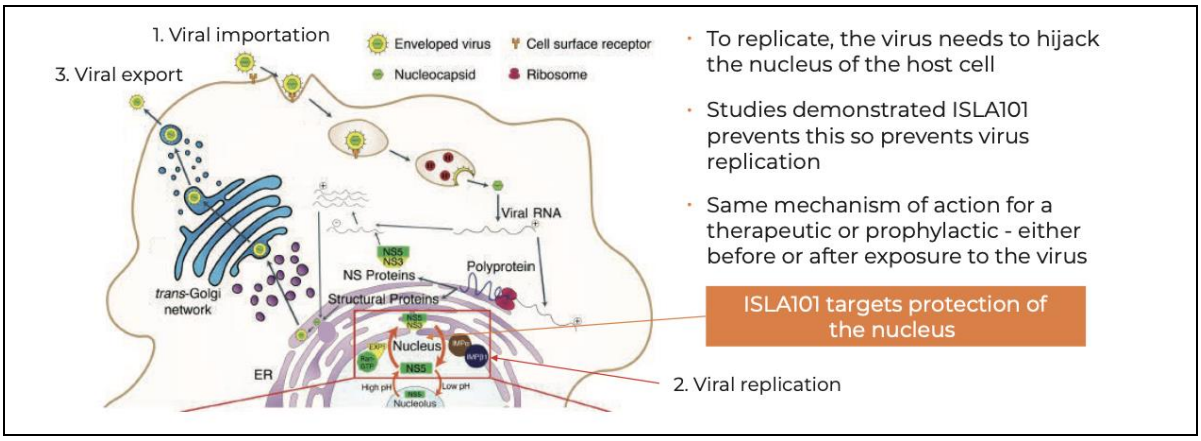
Source: For Zika - Wang et. al. (2017), Nuclear import inhibitor N-(4-hydroxyphenyl) retinamide targets Zika virus (ZIKV) nonstructural protein 5 to inhibit ZIKV infection. Biochem Biophys Res Commun. 2017 Dec 2;493(4):1555-1559. Epub 2017.For Chikungunya: WO 2014/169355.

How ISLA-101 works against flaviviruses

ISLA-101 prevents the nuclear entry of a particular viral protein into the host cell.

Viral importation of flaviviruses occurs at the skin, typically upon a mosquito bite, and through the viral proteins reaching the nucleus of the host cell. ISLA-101 as an NS5 nuclear transport inhibitor prevents the nuclear entry of a particular viral protein into the host cell nucleus. In so doing, it prevents propagation of the viral infection (Figure 4).

Figure 4: ISLA-101's Mechanism of Action



Source: Company

The journey of ISLA-101 post-listing

ISLA-101's ambition post-listing was to take ISLA-101 to a Phase II clinical trial, and it has long worked towards that, but it has taken longer than expected to get to the current point. The company has some achievements to boast of since its listing including:

- Entering into manufacturing agreements with CerRX Inc. and Curia to acquire and process (respectively) the Active Pharmaceutical Ingredient for the trial,
- Executing a contract with the Research Foundation for the State University of New York (SUNY) for the PEACH trial,
- A US$1.3m Congressionally Directed Medical Research Programs (CDMRP) grant from the US Department of Defence in July 2023[7], and
- Adding to its patent portfolio (Figure 5).

Figure 5: Island Pharmaceuticals' patent library

Number	Jurisdiction	Title/Protection	Date of Expiry	Date of Granting
11,007,160	USA	Method of viral inhibition	16 April 2034	28 April 2021
11,752,116	USA	Method of viral inhibition	16 April 2034	23 August 2023
18/355,802	USA	Method of viral inhibition	16 April 2034	NA – Allowed 29 August 2024
2014253607	Australia	Method of viral inhibition	16 April 2034	28 August 2019
2019213440	Australia	Method of viral inhibition	16 April 2034	5 August 2021
2021205039	Australia	Method of viral inhibition	16 April 2034	26 October 2023
2945825	Canada	Method of viral inhibition	16 April 2034	15 November 2022
10201708272S	Singapore	Method of viral inhibition	16 April 2034	31 December 2020
112015026243-0	Brazil	Method of viral inhibition	16 April 2034	20 October 2020

Source: Company, Pitt Street Research

There have been some unfortunate delays in the company's clinical trial, but the trial is now ready to commence.

However, the company's proposed clinical trial has been delayed, and it seems that for some investors, seeing the commencement of the trial will be believing.

The proposed Phase II trial was first delayed in September 2021, to Q1 of CY22, due to an inventory error at a third-party storage facility resulting in less API to purchase than had been originally expected. Island eventually switched manufacturers to Sofgen, a softgel manufacturer in Florida, which resulted in a delay to early 2023, even though the material was manufactured successfully. In December 2022, Island submitted an Investigational New Drug (IND) Application to the FDA, but that IND was not approved as had been anticipated. Instead, the FDA put ISLA-101 on Clinical Hold and specified that changes would need to be made to the trial's protocol and the dosing schedule. The company was requested to conduct a clinical trial prior to Phase

[7] Island did not receive this grant, SUNY did. However, Island is the beneficiary of it as it is directly paying for some of the PROTECT study.

2 in order to determine the appropriate dose. The FDA's issue was that, with the new softgel, it was not clear what level of drug would be delivered into the body.

Island consequently undertook a Single Ascending Dose Study and completed it in early 2024. The study measured blood concentration of ISLA-101, following administration-increasing doses of ISLA-101. This study was a success. Most importantly, it identified ideal Phase 2 dosing (300mg/m2 twice daily) with a high degree of confidence. Moreover, it reinforced the drug's safety and tolerability and showed ISLA-101 achieved blood concentrations that were demonstrated to be effective against dengue. Crucially, the study will allow the upcoming study to be conducted as a single dose rather than as a multi-ascending dose study, leading to significant safety, time and cost efficiencies. Accordingly, the upcoming trial was redesigned. Having looked at the data on bioavailability, where the drug was administered to test subjects who had fasted as well as eaten a high calory meal, Island is now confident that drug bioavailability will match or exceed the effective concentrations of drug seen in the earlier pre-clinical work. The company submitted the protocol to the FDA in July, and clearance was finally given in early-August 2024.

The PROTECT trial

ILA has commenced its long-awaited Phase 2 study PROTECT.

ILA has commenced its long-awaited Phase 2 study. The study was renamed PROTECT, short for PROphylactic and TrEatment Challenge Trial, following the redesign of the trial to a prophylactic and therapeutic strategy. ILA is collaborating with the US Army to use its Dengue Human Infection Model (DHIM), with the Army manufacturing and providing an attenuated strain of the dengue virus that subjects will be exposed to.

PROTECT has commenced now that the 2024 mosquito season Is ended to ensure that the public is protected from unwanted transmission of the virus. Nonetheless, patient screening for the trial commenced in August and the first cohort will be pre-treated as early as late September, immediately prior to their exposure to the attenuated challenge virus once the mosquito season is officially over.

There will be 2 cohorts: An A cohort with 4 subjects randomized 3:1 (Active:placebo) & the B cohort (Phase 2b) that will include 10 subjects randomised 8:2 (active:placebo). The A cohort is a prophylactic or preventative arm, whilst the B cohort will be a preventative arm. It will be done at SUNY Upstate Medical Hospital in Syracuse. The trial will cost around US$1.1m. The trial is being aided with US$625,000 in funding from a Congressionally Directed Medical Research Programs grant, allocated by SUNY Upstate New York. Island Pharmaceuticals also has a CRADA (Cooperative Research and Development Agreement) in place with the US Army for ISLA-101.

The company will have results from the first cohort by the end of CY24.

The fast pace of Dengue's spread and ISLA-101's mechanism means the company will have results from the first cohort by the end of CY24. A Phase 2b cohort will begin being dosed in January 2025. Results from the trial are expected in the first half of CY25, following which the company will conduct an end of Phase 2 meeting with the FDA. During and after the trial, the company will have ongoing discussions with potential partners for commercialisation as well as for research.

As the small number of test subjects will have suggested, this trial is not powered to show statistical significance. That powering will come in Phase 2b. That said, infectious disease studies historically have tended to translate well

from a pre-clinical to a clinical setting, so it's reasonable to expect some good data from Phase 2a, particularly on a meta-analysis.

What will happen after the PROTECT trial?

We expect any positive results from the trial to be significantly accretive for the creation of shareholder value.

This will depend on the results of the trial. We expect any positive results from the trial to be significantly accretive for the creation of shareholder value. Investor sentiment towards this stock will rally in the short-term, and it will also be a sign for interested commercial partners to follow through on their interest. It is likely that a Phase 3 trial will be needed, but this could potentially be shorter than the usual Phase 3 trial just like Phase 2 will be, given the nature of Dengue fever. Nonetheless, such a trial would be more lengthy than Phase 2 on account of the larger number of patients that could be required. We will not discern exactly how long it could take.

ILA's PRV will mean in the event ISLA-101 is approved by the FDA, ILA could expedite the approval process for another drug or sell the voucher to another company.

ILA is fortunate that the ISLA-101 program currently is eligible to receive a Priority Review Voucher (PRV) upon approval. This will mean that in the event ISLA-101 is approved by the FDA, the company will be permitted to expedite the approval process for another drug or sell that voucher to another company. PRVs can sell for over US$100m – as judged by the ten most recent PRVs. It goes without saying that such a non-dilutive cash injection would be spectacular for the company.

It goes without saying that negative results from the trial – a failure to hit the primary endpoint – will be a major setback for the company. Dependant on the extent to which the endpoint is missed, the company may try to conduct another trial with a different dosage, or it may pivot to other indications. Such a pivot would not prevent negative investor sentiment towards the company, however.

Even in the event of positive results from the trial, there is the risk that the data or the submission may not be acceptable to regulators such as the FDA. It may order the company to conduct another trial or ask for further clarification in the form of a Complete Response Letter (CRL). As the recent case study of Cyclopharm (ASX: CYC) depicts, a CRL may be issued even when the clinical data is overwhelmingly positive, but where there may be questions about issues that may appear trivial in comparison to the safety and efficacy data. Examples may include labelling issues or manufacturing concerns.

All this being said, the main concern for investors should be the outcome of the clinical trial, and even though clinical-stage biotechs involve a high degree of risks (see p.22 for a broader outline of the key risks), investors can have a higher degree of confidence because the data to date has been overwhelmingly positive.

The Scourge of Flaviviruses

The term flaviviruses is often used to allude to viruses transmitted by mosquitos.

The term flaviviruses is often used to allude to viruses transmitted by mosquitos. Technically speaking, flaviviruses are any positive-stand RNA viruses in the family Flaviviridae. These viruses tend to be arthropod borne (by mosquitos, but other parasites as well, such as ticks), although the correct term for viruses specifically transmitted from mosquito bites, regardless of strain, is arboviruses. However, all the diseases ILA is targeting fall under the category of flaviviruses so we will continue to use this term.

Many of the points we will make about Dengue – specifically how it spreads and why the incidence of dengue is on the rise – are relevant to other flaviviruses too. But Dengue is one of the more challenging because of its far larger worldwide prevalence and the difficulty in developing or procuring vaccines or treatments.

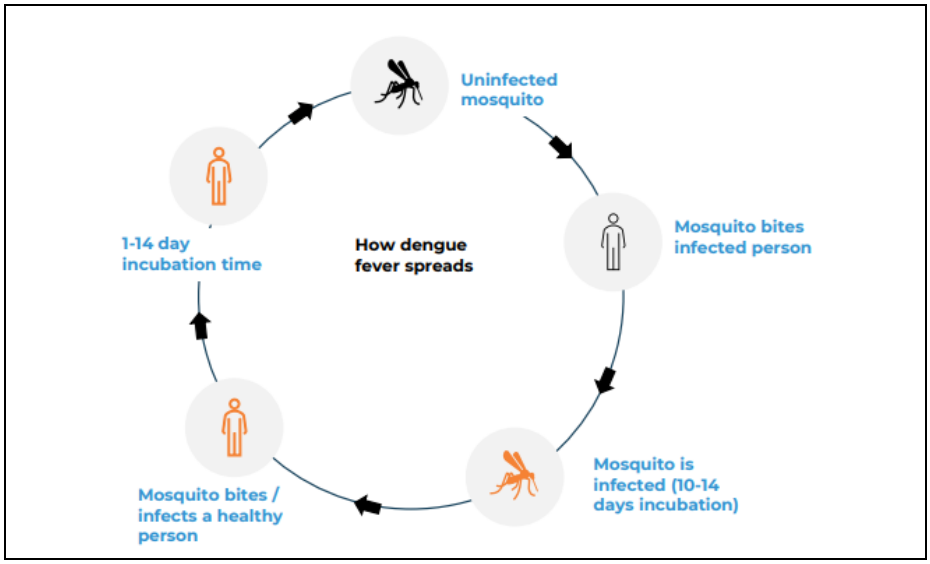
Dengue

There are 4 known serotypes of Dengue. Any vaccine would need to protect against all four strains, and this is why vaccine development has been so difficult.

Dengue (pronounced 'deng-gey'[8]) is a viral infection spread by two species of mosquito, *Aedes aegypti and Aedes albopictus*. There are 4 known serotypes of Dengue (DENV-1, DENV-2, DENV-3 and DENV-4) and infection with one serotype is thought to confer lifelong type-specific immunity. However subsequent infections with different serotype may result in haemorrhagic fever and even death. Any vaccine would need to protect against all four strains of dengue, and (as we will come to shortly) this is why vaccine development has been so difficult.

Dengue affects infants, children and adults with symptoms developing between 3 and 14 days of a mosquito bite (Figure 6). There is a risk of dengue transmission through blood transfusions, tissue transplants or organ donations, but Dengue is not known to be spread through contact with naked, unwounded skin, with aerosol droplets or via sexual context (unless blood is involved)[9].

Figure 6: ISLA-101's efficacy against other flaviviruses



Source: Company

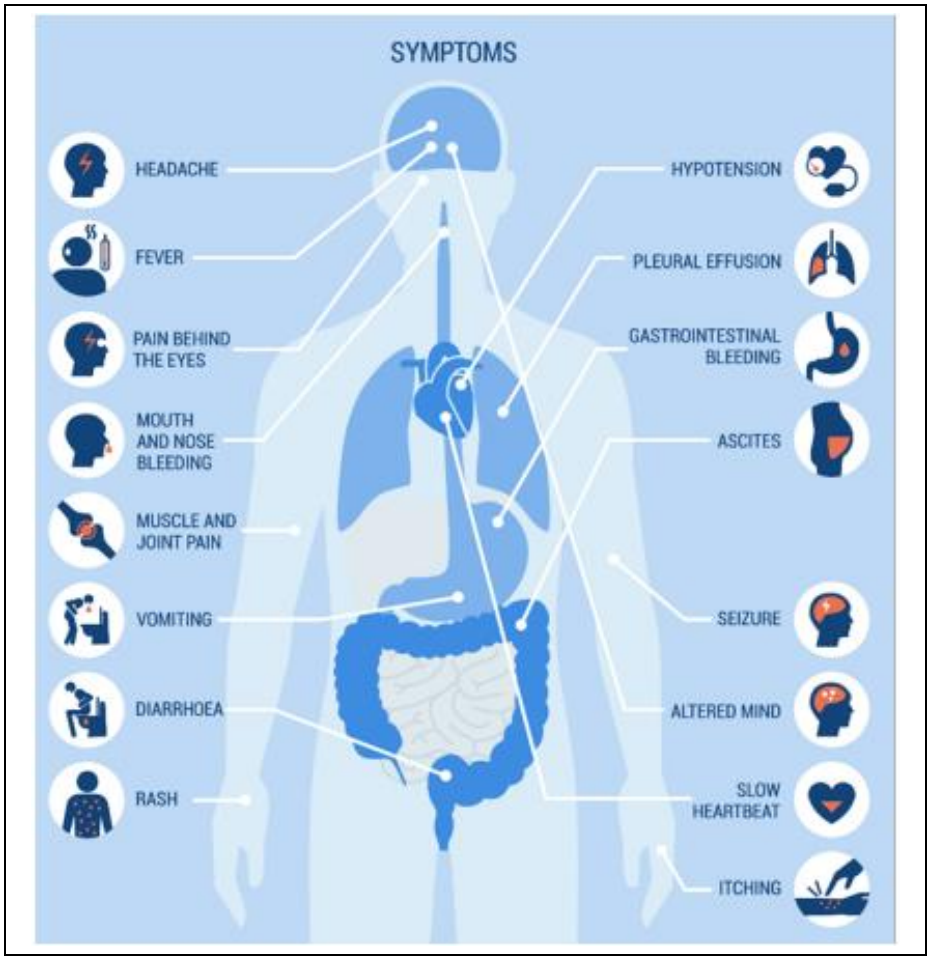
[8] The name is possibly African in in origin, from the Swahili word 'denga', meaning 'bone pain' or 'severe pain', referring to the severe joint and muscle pain associated with the disease. See *How Did Dengue Get Its Name?* by Allyse Smith and Jason Socrates Bardi, Think Global Health, 17 January 2020.
[9] https://www.cdc.gov/dengue/training/cme/cmm/page45901.html

Dengue can cause several symptoms including headaches, gastrointestinal bleeding, a reduction in blood platelets, seizures, itching, rashes and vomiting.

Dengue can cause several symptoms including headaches, gastrointestinal bleeding, a reduction in blood platelets, seizures, itching, rashes and vomiting (Figure 7). Since 2009, dengue has been classified by the WHO by degrees of severity. Severe dengue is defined by the presence of severe plasma leakage, severe bleeding or severe organ involvement.

Some individual symptoms can cause health complications in and of themselves. Take the reduction in blood platelets for example. It happens because the virus suppresses bone marrow, increases platelet destruction by the immune system, and causes platelets to be used up in the micro blood clots and sequestered in the spleen. The fall in blood platelets reduces the risk of blood clotting but increases the risk of severe bleeding.

Figure 7: Dengue symptoms



Source: Company

Dengue is most frequently reported in the Carribbean, Central America, South America and Southeast Asia. But there have been increased incidences of Dengue in regions not traditionally known as hotspots.

Dengue occurs worldwide, but is most frequently reported in the Caribbean, Central America, South America and Southeast Asia. Nonetheless, there have been increased incidences of Dengue in regions not traditionally known as hotspots. In the United States during the last 12 months, there has been increased attention towards the virus given:

- A public health emergency was declared in Puerto Rico,
- The first ever locally acquired case of dengue was reported in Pasadena, California

- there were nearly 200 cases of dengue in New York and New Jersey in the first 6 months of 2024.

This led to the CDC issuing a Health Advisory Network (HAN) Health Advisory[10] and launching a program-led emergency response.

Turning to Australia, after an absence of Dengue between 1955 and 1981, there have been several outbreaks from each of the serotypes ever since. The primary vector is the *Aedes aegypti* mosquito that is present in northern Queensland. Although there have been some rare cases outside Queensland due to the introduction of infected mosquitos in air cargo, these have not led to any further establishment of the vector or the virus. There has been a rise in incidence of Dengue in 2024, although these have mostly been acquired from travellers returning from Indonesia and restricted to north and central Queensland and Western Australia, although there has been sporadic transmission.

Other flaviviruses ISLA-101 could target

It would be beyond the scope of this report to cover all mosquito-borne viruses, but we will go over those which Island Pharmaceuticals has mentioned as indications it could target in the future. As we noted in the third of our Key Reasons to take a look the company, it could be quicker to obtain approval for ISLA-101 against these indications once approved for Dengue, because the virology of these viruses is similar.

- **Zika** is probably the most well-known flavivirus just because of the 2015-16 epidemic that the World Health Organisation declared to be a Public Health Emergency of International Concern. Zika was first identified in rhesus monkeys in Africa in 1947 and has circulated in Africa ever since. It was first identified in Asia in 1966 and it has reached as far as the Caribbean and Polynesia, but there have only been occasional outbreaks. Like Dengue, it is spread through *Aedes aegypti* and *Aedes albopictus* mosquitos[11].

  The highly publicised 2015-16 outbreak of Zika actually pales in comparison to the ordinary annual spread of Dengue.

  The spread of Zika during the 2015-16 outbreak was only a fraction of the annual spread of Dengue (with over 1 million in Brazil alone during the outbreak versus 100-400 million Dengue infections every year[12]), although it overturned prior perception that Zika was a milder disease that tended to be self-limiting and if symptomatic, would not get much worse for patients than having an itchy rash and mild joint pains. There was evidence from the outbreak that the virus could be transmitted from a pregnant woman to her fetus and could cause significant birth defects and neurological problems. Moreover, that outbreak was the first time the transmission of zika via sexual contact and blood transfusions was demonstrated[13]. The 2015-16 outbreak was a reason for many athletes to skip the 2016 Olympics in Rio de Janeiro[14].
- **Yellow Fever** is the second most prevalent flavivirus, so-called because of the effect of a patients' skin turning yellow – this known as jaundice and occurs when the infection involves the liver. Is spread through several species of mosquitos of the genus Haemagogus.

  Yellow fever is endemic in 34 countries in Africa and 13 countries in Central and South America. There are vaccines for yellow fever which are

[10] https://www.nyc.gov/assets/doh/downloads/pdf/han/advisory/2024/han-advisory-17.pdf
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5800195/
[12] CDC and WHO data
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5800195/
[14] See *The Zika virus is just the latest challenge facing the Rio Olympics* by Vincent Bevins, the Los Angeles Times, 9 February 2016.

believed to last for life. The receipt of a yellow fever vaccine is commonly a travel requirement for visitors travelling to or from endemic countries. It does not occur naturally in Australia although mosquitos capable of transmitting the virus are present in North Queensland.

- **West Nile virus** is also a member of the family Flaviviridae. The Nile it is named after is actually the West Nile district of Uganda (where the virus was discovered) rather than Egypt's Nile River. It is a milder version of the disease but there is no human vaccine or specific treatment and it is among the most common Flaviviruses in Western countries.
- **Chikungunya virus** (pronounced Chik-un-Gun-yuh) is a mosquito borne alphavirus. It is named after a word in the Kimakonde language, meaning 'to become contorted'. In the last 20 years, outbreaks have become more frequent and widespread, having been identified in over 100 countries. There are several vaccines being developed but are yet to be licensed or commercialised.

One virus that is endemic to Australia but is not a focus of Island Pharmaceuticals at this stage, is Murray Valley Encephalitis Virus (MVEV), endemic in the Kimberley region of WA and the Top End of the NT, but cases have been reported in some parts of south-eastern Australia in early 2023.

Another is Japanese encephalitis virus (JEV), called Japanese because the first ever case was documented in Japan in 1871. In February 2022, a cluster of locally acquired JEV infections occurred in south-east Australia, picked up from stillborn pigs. There are several vaccines available[15] - although in Australia none are funded under the National Immunisation Program or by states and territories.

Flaviviruses are often misdiagnosed (as other flaviviruses or other illnesses) because their symptoms are similar and the only real difference is the specific RNA virus.

All of these viruses are often misdiagnosed (either as other flaviviruses or other illnesses) because their symptoms are similar and the only real difference is the specific RNA virus, which can only be detected in specific tests for the purpose of identifying the strand of virus, with PCR tests of medical samples being one such example[16]. And as one would expect, the priority for healthcare professionals should be treating the patients rather than seeing the specific DNA strand. Even though it is a requirement in many jurisdictions to record incidences of certain diseases, there may still be potential to misdiagnose diseases.

What about Malaria? Is it of any relevant to Island Pharmaceuticals' endeavours? Malaria is parasitic and not a virus.

What about Ebola? It belongs to a different family of viruses – specifically filoviridae – and its natural host is fruit bats. It is therefore not relevant to ISLA-101 but is relevant to the company's galidesivir project (see Appendix I for further details).

[15] Australian Immunisation Handbook
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10258378/

Dengue is on the rise

In 2023, the largest ever number of dengue cases was recorded…and 2024 has been even worse

In 2023, the largest ever number of dengue cases was recorded with 4.5m cases and 2,300 deaths in the Americas alone. 2024 has been even worse. The World Health Organisation has had 10.4m suspected cases of dengue referred to it in the first 6 months of 2024, and that is just from the Americas. It is 232% more than the same period last year[17].

It is a major societal problem being endemic in over 100 countries and infecting 400 million people annually. Of these, 100 million show symptoms and 40,000 die. The UN OCHA described 2023 as a horror year for dengue. Symptoms can last for a week, but patients can be asymptomatic and can suffer twice, with symptoms worse the second time around.

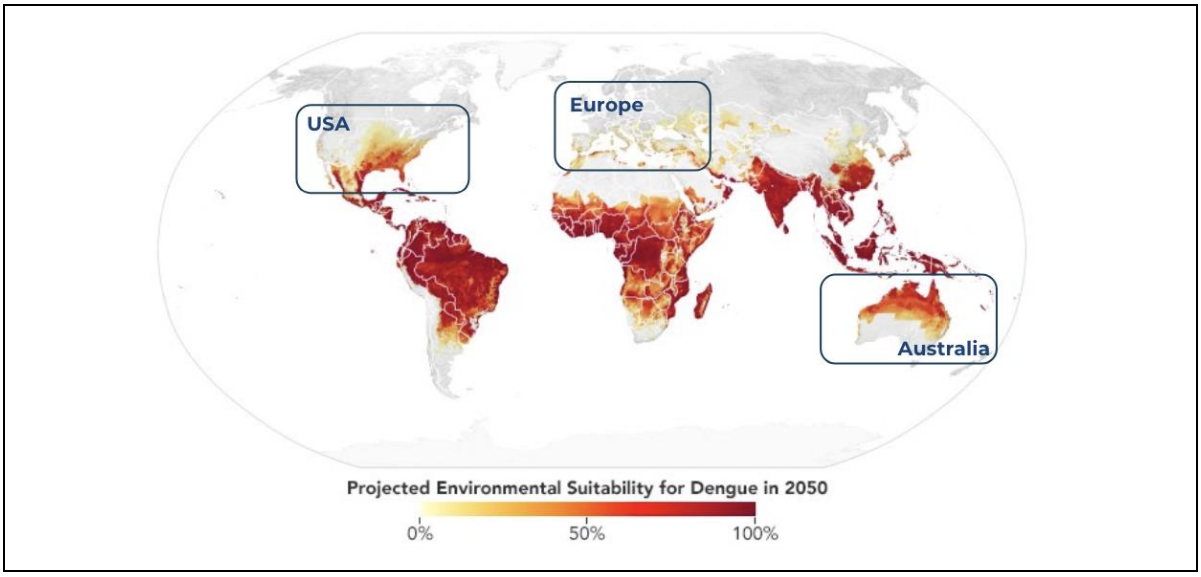
There are several symptoms including (but not limited to) headaches, fever, pain, hypotension, gastrointestinal bleedings, seizures, itching, slower heartbeat, rashes, diarrhoea, vomiting and nasal bleeding. In the US, hospitalisation tends to cost US$7,000 per patient. There are no pharmaceutical treatments that directly attack the fever (just symptomatic relief medicines like paracetamol or general mosquito repellents like sprays and bets), and the problem is expected to get worse in the future.

Why is Dengue expected to get worse?

The incidence of Dengue is expected to get worse because of climate change and increasing urbanisation.

Because of climate change and increasing urbanisation. Already 50% of the world's population is at risk and this figure expected to increase (Figure 8). Warmer temperatures accelerate the mosquito population by increasing breeding activity, reducing incubation time for mosquitos to become infectious and allowing them to survive longer through winter. Humidity has a particular impact on improving mosquitos' chances of survival.

Figure 8: Projected environmental suitability for dengue in 2050



Source: NASA Earth Observatory map by Lauren Dauphin based on data from Janey Messina, University of Oxford - https://earthobservatory.nasa.gov/features/disease-vector

[17] World Health Organisation Data

The Rockefeller Foundation estimates that dengue will impact 60% of the world's population by 2080.

The Rockefeller Foundation estimates that dengue will impact 60% of the world's population by 2080 and Zika will threaten an additional 1.3 billion by 2050[18].

Flaviviruses have *already* grown over the past few decades due to climate change. It has been estimated that dengue's incidence has grown 30-fold over the last 50 years[19]. This has been due to the same trends expected to make the incidence of flaviviruses worse than they already are, as well as the lack of treatments for it.

But aren't there any treatments for Dengue?

There are no direct treatments, only treatments that aid symptoms, but do not fight the disease itself.

There are no direct treatments, only treatments that aid symptoms, but do not fight the disease itself. The only approved vaccine in the United States and Australia is one only approved for secondary dengue infections - Sanofi Pasteur's **Dengvaxia**. Although it is approved in Australia and the USA (among other jurisdictions), it is never prescribed for primary infection, is only recommended for people between the ages of 9-45, doesn't protect against all strains and there is some controversy with the clinical trial that led to its approval. According to an April 2024 article in the Journal of Travel Medicine, just 90 doses of the vaccine were imported into Australia during the near 7 years between Dengvaxia's July 2017 TGA approval and the article's publication[20].

Takeda Pharmaceuticals has a vaccine of its own - **TAK-003**. The vaccine is a live-attenuated vaccine containing weakened versions of the four serotypes of the virus that cause dengue. TAK-003 has passed a 4.5-year Phase 3 study in over 20,000 children and adults. The vaccine is approved in the EU, UK, Brazil, Argentina, Indonesia and Thailand. In May 2024, TAK-003 received prequalification from the World Health Organisation, making it only the second vaccine to be prequalified by the WHO.

However, TAK-003 does not equally protect against all strains and progress for its approval in the US has stalled. In July 2023, Takeda withdrew the US Biologics License Application (BLA) for TAK-003 following discussions with the FDA on aspects of the data that were unable to be addressed within the current cycle[21].

Two other vaccines in development are **TV003 and TV005** from the National Institute of Allergy and Infectious Diseases. Both are still in clinical development but have been licensed out to various manufacturers in preparation for its future approval[22]. The problem is that these trials require a lengthy follow-up (3-5 years) from the WHO because of guidelines from the WHO needing baseline blood samples from participants for efficacy stratification by serostatus and the need for a three-to-five year follow-up to identify potential safety risks, which may occur about 3 years after vaccination[23]. These guidelines are not necessary for controlled human infection models (CHIMs).

J&J is developing a treatment – **JNJ-1802** (or mosnodenvir), which is an oral antiviral. It has a different mechanism of action but has shown promising results in a Phase 2a trial that read out in October 2023.

[18] https://www.rockefellerfoundation.org/insights/perspective/the-increasing-burden-of-dengue-fever-in-a-changing-climate/
[19] Ibid.
[20] https://academic.oup.com/jtm/article-abstract/31/4/taae052/7641505
[21] https://www.takeda.com/newsroom/statements/2023/takeda-announces-voluntary-withdrawal-of-US-biologics-license-application-for-dengue-vaccine-candidate-TAK-003/
[22] https://www.jci.org/articles/view/177610
[23] Ibid.

There is an urgent need for further treatments and ISLA-101 can play a part in it. Please see our valuation section for our own estimations of the potential market opportunity for Dengue fever.

ILA's leadership team

The composition of the current Board of Directors and Advisory Board is as below (Figures 9 & 10).

Figure 9: Island Pharmaceuticals' Board of Directors

Name and Designation	Profile
Paul MacLeman Executive Chairman	Dr Paul MacLeman brings decades of experience across the life sciences sector, including veterinary practice, pharmaceutical development and manufacturing, biotechnology, diagnostics and finance. He has expertise in capital raising, business development, technology commercialisation, and drug development. He has founded life sciences start-ups in the biologics area and worked in investment banking. He previously served as Managing Director and/or CEO of several VC funded, ASX, NASDAQ and TSX listed companies. Paul is the current Chairman of AdAlta Limited (ASX: 1AD). He is a Fellow of the Australian Institute of Company Directors.
David Foster Executive Director	Dr Foster has 20+ years' experience in life sciences representing pharmaceutical, biotherapeutic and diagnostic companies, while in private legal practice. He served as intellectual property counsel at Medarex, a mid-sized biotherapeutics company, acquired by Bristol-Myers Squibb. Dr Foster co-founded Roberts Foster LLP - a technology focused law firm, bionorthTx- a regional life science trade association, and multiple private biotechnology companies. He is a board member of bionorthTx and private biotechnology companies and is a Member of Australian Institute of Company Directors. He holds a Ph.D. from The University of Texas Southwestern Medical Center and J.D. from Golden Gate University School of Law.
Chris Ntoumenopoulos Non-Executive Director	Mr Ntoumenopoulos has more than 20 years' financial markets experience. He is Managing Director at Twenty 1 Corporate, an Australian-based corporate advisory firm. He was a founding director of both ResApp (ASX: RAP), which was acquired by Pfizer, and Race Oncology (ASX: RAC), which is also repurposing a drug. Currently he serves as a Non-Executive Director at TrivarX (ASX: TRI) and Tryptamine Therapeutics (ASX: TYP).
Albert Hansen Non-Executive Director	Mr Hansen is the Managing Partner at KESA Partners. He brings decades of experience in healthcare and investment, including Managing Director of Signet Healthcare Partners, serving on investee companies as Chairman, Director and Interim CEO of pharmaceutical companies and CROs. Mr Hansen has substantial senior investment banking experience at firms such as Darby Overseas Investments, Dillon Read and E. F. Hutton. Former Director - Corporate Finance US Treasury, and retired Captain, U.S Army Special Forces.
Anna Lavelle Non-Executive Director	Dr Lavelle is Chair of Medicines Australia; previously CEO and Executive Director of AusBiotech Ltd. and the Australian Red Cross. Director, Research Australia, the Agricultural Biotechnology Council of Australia and the Advisory Board for the School of Biological Sciences at Monash University. She has Chaired, or been a member of, various Federal and State government advisory committees. She holds a PhD in Genetics from the University of Melbourne and is a Fellow of the Australian Academy of Technological Sciences and Engineering.

Source: Company

Figure 10: Island Pharmaceuticals Scientific Advisory Board

Name	Profile
Dr Leigh Farrell	Dr Farrell has over 30 years' experience in the biotechnology and pharmaceutical industry and is Head of Health Security Systems Australia, a Division of DMTC Ltd, is a non-executive director of Pro Medicus Ltd, Ena Respiratory Pty Ltd and Axelia Oncology ty Ltd, and is a member of the Walter and Eliza Hall Institute of Medical Research Board Commercialisation Committee and a member of the Independent Advisory Council of Medicines Australia. His past appointments include: Senior Vice President, Commercial at Certara USA, Inc where he was responsible for Asia Pacific Commercial and global government engagement for the preparedness, planning and response to major health emergencies; Chairman & COO of d3 Medicine, LLC; Vice President of Business Development at Biota Pharmaceuticals Ltd, Research Manager Johnson & Johnson Research and CEO of Gene Shears Pty Ltd. Leigh holds a PhD in Biochemistry and a Bachelor of Science (Honours) from Monash University and is a Fellow of the Australian Institute of Company Directors.
Prof Stephen Thomas	Professor Thomas, served as the Lead Principal Investigator for Pfizer/BioNTech global Phase III COVID-19 vaccine trial. Prof. Thomas is a world-renowned virologist and vaccinologist and has authored numerous papers and articles on dengue fever, Zika and many other infectious diseases. His past appointments include Chief of the Division Of Infectious Diseases at New York Upstate Medical University; Professor of Medicine, Professor of Microbiology & Immunology, and Infectious Diseases physician-scientist from the State University of New York (SUNY), Upstate Medical University; and the Chief of the Division of Infectious Diseases and Director at the Institute for Global Health and Translational Science (IGHTS).
Amy Patrick	Dr Patick is a scientific consultant with deep expertise in antiviral drug discovery, development and viral resistance with broad know how in emerging virus epidemics and translational medicine. Previously, Dr. Patick has served as Vice President, Research at Adamas Pharmaceuticals, Vice President, Biological Sciences at Genelabs Technologies, Head of the Antiviral Biology Therapeutic Area at Pfizer, Inc. and Research Scientist at Bristol-Myers Squibb Company. Dr. Patick has also served as President for the International Society of Antiviral Research. Dr. Patick was a postdoctoral fellow in immunology at the Mayo Clinic/Foundation in Rochester, MN and received her PhD in Medical Microbiology from the University of Wisconsin, Madison.

Source: Company

Our Valuation of Island Pharmaceuticals

We have derived a value of A$83.0m in our base case and A$109.1m in our bull case, which is $0.31 per share and $0.12 per share respectively under the current number of diluted shares on issue.

We have valued Island Pharmaceuticals using a Net Present Value (NPV) Approach, assuming success in the forthcoming clinical trials and eventual commercialisation with a licensing model. We have derived a value of A$59.9m in our base case and A$80.3m in our bull case, which is $0.31 per share and $0.42 per share respectively under the current number of diluted shares on issue (265.4m) (Figure 12 and Appendix III). The key assumptions driving our DCF valuation are outlined below and summarised in Figure 11):

- **We assume Island passes Phase 2 (the PROTECT trial) then commences Phase 3 within 12 months from now, then obtains FDA approval in mid-FY28 and has a 7-year period of market exclusivity**. Accordingly, our model ends at the end of FY35 and there is no terminal growth.
- **A licensing model with milestone payments and royalties on sales.** We have assumed ILA finds a licensing partner in the next 12 months, once Phase 2 is complete and assuming a successful result. Such a deal would involve upfront and milestone payments (totalling US$70m) and a 20% royalty on all sales. Specifically, we assume US$10m on signature of the deal, US$15m on commencement of Phase 3, US$40m upon read-out of Phase 3 results (again, assuming a successful result) and US$15m upon approval. We assume Island bears US$40m in development costs and then has cash costs worth 40% of its royalty sales. We have consequently not assumed any further external capital is raised by ILA other than payments received from the licensee, although using the diluted shares on issue accounts for the exercise of all options and performance rights on the table right now.
- **We assume a total patient population of 10m to start with followed by 3% growth per annum.** The starting figure is derived from CDC data roughly estimating the number of patients in the Americas region during CY24[24]. This includes North, Central and South America as well as the Caribbean. We assume gradual ramp up over our model and that ILA reaches 8% of that market by the end of the life of our model, which would equate to just over 1.1m patients. We assume the company would be able to use the same regulatory dossier used to gain FDA approval to appease regulators in other countries in the Americas.
- **A treatment price of US$1,000**. We acknowledge this might be a contentious because there are several estimates for what current Dengue treatments cost, because there aren't any – any 'treatments' only relieve symptoms anyway. We have gone with an estimate from an article the American Journal of Tropical Medicine and Hygiene which has estimated the out-of-pocket costs and indirect costs to equate to nearly US$1,000 per 'episode'[25]. If ISLA-101 proves that it can work against Dengue, the company could charge a premium over existing treatments.
- **A corporate tax rate of 30%** in line with Australia. We acknowledge corporate tax rates are lower in the US and other potential jurisdictions for ISLA-101, although the company would have to pay corporate tax in Australia too and lower rates elsewhere may not be enough to offset liability here.
- **A discount rate of 14.7%.** This is derived from a 4% risk-free rate of return, a 7% equity premium and 1.5x beta.

[24] https://emergency.cdc.gov/han/2024/han00511.asp
[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6553920/

Figure 11: Our modelling assumptions for Island Pharmaceuticals

Model Assumptions	Base	Bull
Launch	FY28	FY28
Estimate market size (patient numbers)	10,000,000	12,000,000
Growth	3.0%	3.0%
Potential market penetration	8.0%	8.5%
Realised price (US$)	1,000	1,000
Peak sales (US$m)	1,533	1,954
Peak royalty revenue (US$m)	307	391
Gross milestone revenue (US$m)	80	80
Commercial exclusivity period (years)	7	7
Drug development cost (US$m)	40	40
Partner's share of costs	50.0%	50.0%
Discount rate	14.7%	14.7%
Royalty rate	20.0%	20.0%
Tax rate	30.0%	30.0%
Probability of success	50.00%	50.00%
Risk-adjusted NPV (A$m) - base case	83.01	109.10
rNPV per share (A$) - base case	0.313	0.411

Source: Company

Figure 12: Our modelling assumptions for Island Pharmaceuticals

ISLA-101 Valuation	Base	Bull
NPV (US$)	$ 104,596,288	$ 137,468,583
Risk Factor	50%	50%
rNPV (US$)	$ 52,298,144	$ 68,734,291
AUD/USD	0.63	0.63
rNPV (A$)	**$ 83,012,927**	**$ 109,102,050**
Shares on issue (diluted)	265,357,245	265,357,245
Implied price	**$ 0.313**	**$ 0.411**
Current share price	$ 0.190	$ 0.190
Premium	*65%*	*116%*

Source: Company

Our base/bull case differences

The key differences to our bull case are (Figure 11):

- A 8.5% market share as opposed to 8% in our base case, and
- A 20% larger market size, 12m to begin with but growing at the same pace (2% per year).

Key Risks facing Island Pharmaceuticals

We see the risk of failure of the PROTECT trial as the key risk facing the company. A failure of the clinical trial would essentially send the Company back to 'Square One', spelling the likely death knell for ISLA-101's commercialisation against flaviviruses.

Other risks include:

- **Regulatory risk**. There is a risk that ISLA-101 may not be approved by regulators. Even if data suggests efficacy, the FDA may not find the data acceptable, or decline to approve ISLA-101 on other grounds such as the potential for negative interaction with other drugs. Even when approved, there is the risk that approval may be withdrawn, or that further regulations may be imposed on the company to be able to continue to market, manufacture and/or produce the drug.
- **Market acceptance risk**: There is the risk that even if the drug passes clinical trials, it will fail to be approved and/or attract a strong following in its applicable markets.
- **Key personnel risk**. There is the risk that the company may lose key personnel and be unable to replace them and/or their contribution to the business.
- **Capital risk**. There is the risk that the company may need to undertake future capital raisings. There is no guarantee that the company will be able to raise such capital, let alone on favourable terms. Even if successful, this would be 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 the Australian Securities Exchange 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 or medical device stock mentioned on this report, including ILA.

Glossary

Aersolisation – The process of converting a physical substance into the form of particles small and light enough to be carried on in the air as an aerosol.

Angina – A type of chest pain caused by reduced blood flow to the heart.

Bioweapons - Devices or agents used or intended to be used in a deliberate attempt to disseminate disease-producing organisms or toxins using aerosol, food, water, or insect vectors

Chikungunya – An alphavirus spread by *Aedes aegypti* or *Aedes albopictus* mosquitoes. It is named after a Kimakonde language word meaning 'to become contorted'.

Dengue – A viral infection caused by mosquito bites from infected mosquitos.

Efficacious – In the context of clinical trials, this word means the drug worked.

Efficacy – As above, it means the drug worked.

Endemic – A disease regularly occurring in a particular area of community.

Epidemic – An incidence where the number of disease cases increases unexpectedly. Unlike pandemics, epidemics tend to be restricted a specific geographical area, and virology, population immunity and disease severity has an impact on its spread, and there is some degree of predictability.

Flavivirus – A group of viruses that is transmitted to humans by mosquitos, including Dengue and Yellow Fever.

Hypertension – Where pressure in the blood vessels is too high (140/90mHg or higher).

Incubation – The process where a disease is being 'incubated', where it is present in the body but there are no symptoms.

In-vitro – Generally speaking, any event occurring outside the living body and in an artificial environment. In the context of clinical trials, this is work done in a test tube or laboratory dish and not inside a subject's body.

Japanese Encephalitis Virus (JEV) – a flavivirus spread by *Culex tritaeniorhynchus* mosquitos.

Jaundice – Where the skin of someone infected with yellow fever turns yellow.

Live-attenuated – In the context of vaccines, these are vaccines with live pathogens from either a bacterium or a virus that has been 'attenuated' or weakened. These are strong enough provoke an immune response without causing disease and will help the immune system remember the pathogen so it can respond.

Mechanism of Action – How a drug works.

Murray Valley Encephalitis (MVE) – A flavivirus endemic to Australia and PNG.

Nuclear entry – Delivery of molecules into the nucleus of cells. Where DNA viruses deliver their genome into the nucleus of their host cells. This is necessary for viral replication.

Nucleus – The part of a cell that contains all the chromosomes, which encode the genetic material.

Placebo – An alternative treatment used in a clinical trial to compare the drug in question to.

Propagation – The act of widely spreading or promoting something. In the context of this article, flaviviruses.

Prophylactic – A medicine or course of action used to prevent disease.

Serotypes – Groups within a single species of microorganisms. In the case of Dengue, Dengue serotypes are 'different types' of dengue.

West Nile – A flavivirus named after the West Nile district of Uganda, transmitted mostly by species of Culex.

Yellow Fever – A flavivirus, so-called because of the common side-effect of a hosts' skin turning yellow.

Appendix I – Galidesivir and Island's potential biodefense opportunity

Island is currently evaluating a potential biodefence agent called galidesivir. Galidesivir can potentially treat Ebola and Marburg.

Island is currently evaluating a potential biodefence agent called galidesivir. In September 2024, Island signed a binding Letter of Intent with a US company called BioCryst (Nasdaq: BCRX) for the potential acquisition of galidesivir. A non-binding Letter of Intent had been signed back in July. Island will pay BioCryst a US$50k option fee, giving Island exclusive rights to acquire the program for a period of 12 months, enabling due diligence to be undertaken. Galidesivir can potentially treat Ebola and Marburg. This clinical-stage antiviral molecule has a broad spectrum of activity in over 20 RNA viruses, including high-priority threats such as Ebola, Marburg, MERS, Zika, yellow fever and SARS-CoV-2. It is a nucleoside analogue that mimics adenosine triphosphate (ATP) and inhibits viral RNA synthesis, allowing broad activity against many RNA viruses.

The galidesivir program has a robust development history, which commenced initially to target high-priority threats, Ebola and Marburg viruses, then subsequently expanded to include other emerging infectious diseases, MERS and Zika for emergency disease outbreaks. It later evolved to pursue yellow fever as well as SARS-CoV-2. Phase 1 studies have been completed for galidesivir in healthy volunteers, including single ascending dose and multiple ascending dose intramuscular administration studies, as well as intravenous single ascending dose studies. After the completion of due diligence, the parties intend to finalise definitive documents. We understand that Island believes it can potentially get the due diligence done by the end of 2024.

Galidesivir represents part of a major 'biodefense' effort by the US government, to fight 'bioterrorism'. The market opportunity for programmes like galidesivir, should that programme transition to Island Pharmaceuticals, is significant. Indeed, it represents, in our view, a second potential 'company maker'.

What is bioterrorism? Bioterrorism is terrorism where the weapons used are various biological agents. Thankfully bioterrorism has proven rare in recent history, the only notable example being the anthrax attacks of September and October 2001 in the US that resulted in five deaths. However, national security agencies around the world believe that various biological agents have been weaponised by state and non-state actors, and that terrorist groups would use such agents if they could. Of particular concern are anthrax[26], botulism[27], plague[28], smallpox[29], tularemia[30] and various viruses that cause Viral Haemorrhagic Fevers (VHF) such as Marburg and Ebola. An additional concern relates to whether or not the viruses and bacteria have been genetically modified to make their spread more rapid and increase their pathogenicity.

What is biodefence? Biodefense is the development of vaccines and therapeutics that allow governments to protect their citizens from bioterrorism. The idea is that once the drugs or vaccines and developed, they are stockpiled by governments and then rapidly deployed in the event of a confirmed outbreak. The key site for US government biodefense efforts is Fort Detrick, a US Army Futures Command installation located in the town of Frederick, Md, which hosts a biodefence agency called AMRIID, the Army

[26] Caused by *Bacillus anthracis,* a bacterium often found in sheep which, in inhaled, severe breathing problems and death.
[27] A rare poisoning caused by toxins produced by *Clostridium botulinum* bacteria.
[28] The same infection featuring swollen lymph nodes, or 'buboes' that killed a third of the population of Europe in the 1340s. Plague is caused by a bacterium called *Yersinia pestis*.
[29] The dreaded skin disease characterised by fluid-filled blisters caused by the variola virus.
[30] A disease characterised fever, skin ulcers, and enlarged lymph nodes caused by the bacterium *Francisella tularensis*.

Medical Research Institute of Infectious Diseases. Also involved in biodefense in a significant way is BARDA, the Biomedical Advanced Research and Development Authority, which is an agency of the US Department of Health and Human Services (HHS), and NIAID, the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH).

The US government makes considerable ongoing efforts in biodefense. It is estimated that that government spent about US$100bn over the two decades to 2020 on biodefense[31]. With the Covid-19 outbreak having increased public awareness of the need for pandemic preparedness, it's reasonable to expect continued strong spending.

The US government frequency uses trusted private sector drug and developers in biodefence, often by making grants to companies as well as buying products off those companies to be stockpiled. Those trusted partners do not have to be American. A good recent example was a BARDA grant to Icon plc related to a next-generation anthrax vaccine called AV7909. Icon is headquartered in Dublin. Emergent BioSolutions (NYSE: EBS) was the vaccine's developer but the BARDA money extended to Icon as the clinical research organisation[32].

Biodefence developers often benefit from the Animal Rule in terms of speed to approval.

Biodefence developers often benefit from the Animal Rule in terms of speed to approval. The FDA's Animal Rule, introduced in 2002 in the wake of the US anthrax attacks, allows for the use of pivotal animal model efficacy studies to support FDA approval of new drugs when human clinical trials are not ethical or feasible. The first vaccine approved under the Animal Rule was BioThrax, an anthrax vaccine for which Emergent BioSolutions gained approval in 2015[33]. Obviously, drugs designed to protect against diseases like Marburg or Ebola can't ethically be tested for prophylaxis in human volunteers, so the Animal Rule will apply. The Rule reduces the cost of a pivotal study, but often limits the facilities in which the studies can be done.

Emergent BioSolutions shows the scale of a stockpiling agreement. By 2016, the year after BioThrax gained approval[34], Emergent had already sold US$1.25bn worth of vaccine to the government, and another US$911m deal was signed in December of that year.

Siga Technologies shows how just one biodefense agent can be a company maker. SIGA Technologies (Nasdaq: SIGA) in 2010 received a contract to supply 1.7 million courses of its smallpox drug for the strategic national stockpile, with the base contract worth about US$500m in revenue up to U$2.8m if BARDA picked up all the options included in the contract[35]. The drug, called Tecovirimat, brand name TPOXX, is an antiviral drug that was identified via a high-throughput screen in 2002. It is effective against all orthopoxviruses including the smallpox virus. Tecovirimat was approved by the FDA in July 2018[36] and so far, it's Siga's only product. Siga is currently capitalised on Nasdaq at about US$600m.

Biodefense agents come with Priority Review Vouchers. If approved by the FDA, Galidesivir may be eligible for a Priority Review Voucher. Under section 3086 of the 21st Century Cures Act, the FDA had to establish a new PRV programme[37] for 'material threat medical countermeasures', which included biodefense agents as well as naturally emerging diseases like SARS.

[31] See *The U.S. spent billions of dollars on biodefense. COVID-19 was the attack it never saw coming* by W.J. Hennigan, Time Magazine, 9 October 2020.
[32] See the Icon press release dated 6 October 2022 and headlined *'ICON selected by BARDA to conduct anthrax vaccine clinical trial'*.
[33] Expert Rev Vaccines. 2016 Dec;15(12):1467-1479.
[34] See U*.S. government gives $1B vote of confidence to Emergent BioSolutions' anthrax vax* by Angus Liu, Fierce Biotech, 12 December 2016.
[35] See *SIGA gets nod for $2.8B antiviral contract, shares rocket up* by John Carroll, Fierce Biotech, 13 October 2010.
[36] Expert Rev Anti Infect Ther. 2021 Mar;19(3):331-344.
[37] The third such programme, the other two being for new rare paediatric diseases and for tropical disease treatments like ISLA-101.

Marburg and Ebola currently represent viruses for which there are no approved biodefence agents. These viruses, member of the filoviridae family, cause two of the most severe and highly fatal Viral Haemorrhagic Fevers known to man. Marburg, so called because it was first identified in the German city of that name in 1967, has an average fatality rate of around 50%[38]. Ebola, first identified in 1976 in the Democratic Republic of Congo, is slightly worse at 60%[39]. There have regular Ebola outbreaks in Africa[40] since the 1970s, including the terrible Western African Ebola epidemic of 2013 to 2016. This, combined with the high mortality rate, and the highly contagious nature of infections, makes Ebola in particular a potential bioterrorism agents, but so far there have been no therapeutics. We think success for Island Pharma with galidesivir could reasonably unlock the kind of stockpile contracts previously seen for anthrax and smallpox.

Galidesivir is a drug with a long development history

What is galidesivir? Galidesivir is a drug that is broadly active against several RNA viruses of various families. The drug was originally developed by BioCryst Pharmaceuticals with funding from NIAID. We understand the initial indication was Hepatitis C Virus, but the drug was later successfully applied to filoviruses such as Ebola and Marburg among other viruses. BioCryst was for many years a player in biodefense but has since appeared to de-prioritise that effort in favour of rare diseases, particularly those involving the complement cascade in the innate immune system[41].

What is galidesivir's mechanism of action? Galidesivir is an adenosine nucleoside analogue. Nucleosides are the four 'letters' to be found in the RNA 'message'[42], of which one is adenosine, and analogues are compounds that look similar but are not the same as the original. Nucleoside analogues are basically 'monkey wrenches' that interfere with viral replication because they are incorporated into viral RNA by RNA-dependent RNA polymerase but, lacking 3'-hydroxyl group, cause RNA synthesis to halt because the phosphodiester bond that would link to the next nucleoside can't be formed. Nucleoside analogues have a long history as antivirals, beginning with Vidarabine for Herpes Simplex Virus back in 1976 and continuing with Zidovudine for HIV in 1987[43]. Remdesivir, the celebrated antiviral developed in 2020 to treat Covid-19 infection, is also an adenosine nucleoside analogue[44]. Galidesivir was created by taking adenosine and substituting a carbon for nitrogen at position 7 on the base and nitrogen for oxygen at position 1 on the ribose ring[45].

Galidesivir effectiveness in non-human primates was established a decade ago. Galidesivir, originally called BCX4430, seems to have originated from Biocryst's efforts to develop a nucleoside analogue drug targeting Hepatitis C Virus. However, by around 2012[46] considerable in *vitro and in vivo* evidence had emerged of broad-spectrum activity in multiple viruses, and the company began working with USAMRIID on the Marburg/Ebola application. By 2014 the

[38] Front Microbiol. 2023 Sep 13:14:1239079.
[39] J Infect Public Health. 2024 Jan;17(1):25-34.
[40] 1995 (Kikwit, DRC), 2000 (2000 (Gulu, Uganda), 2002-2003 (Republic of Congo), 2007 (Bundibugyo, Uganda), 2014-2016 (West Africa, primarily Guinea, Liberia, and Sierra Leone), 2018-2020 (DRC) and 2022 (Uganda).
[41] It currently has one approved drug, called Orladeyo, generic name berotralstat, the first oral, once-daily plasma kallikrein inhibitor approved for hereditary angioedema.
[42] That is, the nitrogenous bases that make up DNA and RNA, plus a sugar. The bases are adenine, guanine, cytosine and uracil/thymine (uracil for RNA, thymine for DNA) combined with a sugar - ribose in RNA, deoxyribose in DNA.
[43] Antiviral Res. 2018 Jun; 154: 66–86.
[44] Drug Des Devel Ther. 2020; 14: 3215–3222.
[45] J Infect Public Health. 2016 May-June; 9(3): 220–226.
[46] See the BioCryst press release dated 12 November 2012 and headlined *'BioCryst broad-spectrum antiviral BCX4430 highly effective against yellow fever in a preclinical disease model*'.

two parties had run a study in non-human primates showing that it could protect against Marburg virus, even when administered as late as 48 hours after infection. This work was the subject of a *Nature* paper[47] and was widely reported because of the Western African Ebola epidemic that had started the previous year[48].

Galidesivir is a broad-spectrum anti-viral agent. The 2014 *Nature* Paper established the effectiveness of Galidesivir in multiple viruses. Its effectiveness *in vivo* in yellow fever was shown in 2014[49], against West Nile in 2017[50] and against Zika in 2020[51]. During Covid it was tried out in a Hamster Model of SARS-CoV-2 with favourable results[52]. The Zika data is interesting because it was obtained in non-human primates. As we noted above, there is data on some 20 RNA viruses in nine different families.

Galidesivir has a good safety profile. The safety, tolerability, and pharmacokinetics of galidesivir have been evaluated in two Phase 1 studies, one where the delivery is via intramuscular injection and the other via intravenous infusion[53]. Each study was double-blind, placebo-controlled, dose-ranging studies in healthy subjects[54].

Island Pharmaceuticals can move quickly with Galdesivir? If Island takes on the drug after its due diligence, then it's reasonable to suggest that ample pre-clinical and clinical work already done by BioCryst and the US government can allow Galdesivir's new developer to move quickly to the next Animal Rule clinical study.

Appendix II – Papers relevant to Island Pharmaceuticals

Fraser et. al. (2014), *A nuclear transport inhibitor that modulates the unfolded protein response and provides in vivo protection against lethal dengue virus infection.* J Infect Dis. 2014 Dec 1;210(11):1780-91. Epub 2014 Jun 5.

- This paper, from the Jans laboratory at Monash University, reports the first use of what became ISLA-101, then called 4-HPR, in a lethal animal model of dengue,

Carocci et. al. (2014), *The bioactive lipid 4-hydroxyphenyl retinamide inhibits flavivirus replication.* Antimicrob Agents Chemother. 2015 Jan;59(1):85-95. Epub 2014 Oct 13.

- This paper, from the Yang laboratory at Harvard, reached similar conclusions to the Jans lab on the *in vivo* efficacy of 4-HPR.

Wang et. al. (2017), *Nuclear import inhibitor N-(4-hydroxyphenyl) retinamide targets Zika virus (ZIKV) nonstructural protein 5 to inhibit ZIKV infection*. Biochem Biophys Res Commun. 2017 Dec 2;493(4):1555-1559. Epub 2017 Oct 4.

[47] See Nature. 2014; 508(7496): 402–405.
[48] See, for example, *Ebola drug could be ready for human testing next year* by Richard Harris, reported on NPR's All Things Considered programme on 11 April 2014.
[49] Antimicrob Agents Chemother. 2014 Nov; 58(11): 6607–6614.
[50] Antiviral Res. 2017 Jun:142:63-67.Epub 2017 Mar 21.
[51] Sci Transl Med. 2020 Jun 10;12(547):eaau9135.
[52] Viruses. 2022 Jan; 14(1): 8. Published online 2021 Dec 21.
[53] See NCT02319772 and NCT03800173 at clinicaltrials.gov.
[54] Clin Pharmacol Drug Dev. 2022 Apr;11(4):467-474. Epub 2022 Feb 19.

- This paper, also from the Jans laboratory, showed 4-HPR's effectiveness against Zika *in vitro*.

Pitts et. al. (2017), *Antiviral activity of N-(4-hydroxyphenyl) retinamide (4-HPR) against Zika virus.* Antiviral Res. 2017 Nov:147:124-130. Epub 2017 Oct 16.

- This paper is the Yang lab's work on 4-HPR in Zika *in vitro* an in an animal model of a Zika infection.

Jans and Martin (2018), *Nucleocytoplasmic Trafficking of Dengue Non-structural Protein 5 as a Target for Antivirals*. Adv Exp Med Biol. 2018:1062:199-213d

- This paper reports on the mechanism of action for 4-HPR in Dengue.

Lee et. al. (2018), *Potential effects of climate change on dengue transmission dynamics in Korea.* PLoS One. 2018 Jun 28;13(6):e0199205.

- This paper reports on how warmer temperatures in Asia can increase the potential for more severe dengue outbreaks.

Endy et. al. (2021), *A Phase 1, Open-Label Assessment of a Dengue Virus-1 Live Virus Human Challenge Strain*. J Infect Dis. 2021 Feb 3;223(2):258-267.

- This paper, from State University of New York's Upstate Medical University at Syracuse, reports on a challenge strain called ' 45AZ5' used to clinically test dengue agents, with a 12-subject study showing the strain to produce only an 'uncomplicated dengue illness'.

Wu et. al. (2021*),* *Increasingly expanded future risk of dengue fever in the Pearl River Delta, China*. PLoS Negl Trop Dis. 2021 Sep 24;15(9):e0009745.

- This paper is similar to the Lee et. al. paper above in terms of showing that climate change can increase the potential for more severe dengue outbreaks.

Waickman et. al. (2022), *Evolution of inflammation and immunity in a dengue virus 1 human infection model*. P Sci Transl Med. 2022 Oct 26;14(668):eabo5019. Epub 2022 Oct 26.

- This paper, also from SUNY Upstate, reports on the immune response generated by the 45AZ5 attenuated challenge strain, relevant to the way in which ISLA-101 will work against the challenge strain.

Appendix III – Capital Structure

Class	In millions	% of fully diluted
Ordinary fully paid shares	176.92	67%
Options	88.44	33%
Fully diluted shares	**265.36**	

Source: Company[55]

Appendix IV – Top Shareholders

Shareholder	Shares (m)	% held
Mr Jason Alan Carroll	24.07	9.07%
Dr William James Garner	22.06	8.31%
Kesa Partners	11.00	4.15%
David C Foster	5.65	2.13%
Neville James Miles	4.19	1.58%

Source: Company

[55] The company's capital structure includes 22,777,778 shares to be issued in the second tranche of the placement, subject to shareholder approval.

Appendix V – Analysts' 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 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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