PITT STREET RESEARCH

Island Pharmaceuticals

Key results coming soon

Share Price: A$0.165

ASX: ILA

Sector: Healthcare

1 April 2025

Island Pharmaceuticals (ASX: ILA) is in a Phase II study of its flagship drug ISLA-101 for Dengue fever. While the company already possesses results from the first cohort and there are positive signs, results from the second cohort are expected next month (in April 2025).

Clinical Update from Phase 2b of the PROTECT clinical trial are due in April 2025

The first step of the trial showed anti-Dengue virus activity, although this was in healthy patients exposed to a weakened version of the virus in a prophylactic setting. This means the volunteers were first dosed with ISLA-101 and then infected with the virus. The second phase will see if ISLA-101 can work as a treatment in healthy volunteers who are infected with the weakened version of the virus before taking drug. Positive results here could see the programme proceed to a prophylactic or treatment Phase 2b study in countries with an endemic wild type virus.

The need for Dengue solutions becomes greater and greater by the year

With each year, flaviviruses, like Dengue, become more and more of a problem. According to data from the European Centre for Disease Prevention and Control there were over 14 million confirmed Dengue cases and over 10,000 deaths in 2024. A further 100,000 cases were recorded just in the month of January 2025. These could be just the tip of the iceberg – as we outlined in previous reports, Dengue could impact 60% of the world's population by 2080. There are no direct treatments, only drugs that relieve symptoms. If ISLA-101 can demonstrate ability to fight the virus, this could be a game changer for the world's fight against Dengue, and potentially other Flaviviruses.

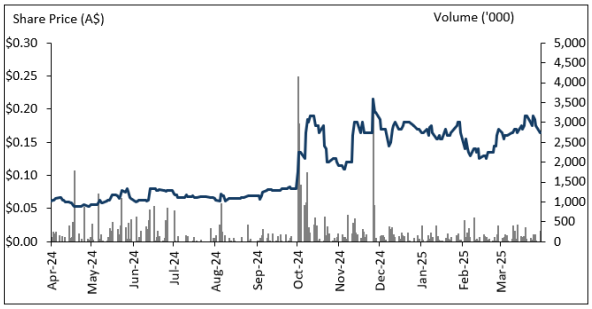
Valuation range of A$0.30-$0.40 per share

We continue to reiterate our valuation of ILA at A$83m in a base case scenario and A$109.1m in an optimistic (or bull) case scenario – currently equating to $0.30 per share and $0.40 per share respectively under the current diluted number of shares on issue. We expect the results next month to be critical as to whether the company can re-rate. A failure of the trial is the key risk facing this stock, something that could lead to the company abandoning its ambitions. Please see p.8 for further risks associated with an investment in ILA.

Market cap. (A$ m)	31.7
# shares outstanding (m)[1]	192.3
# shares fully diluted (m) [1]	276.1
Market cap ful. dil. (A$ m)	45.6
Free float	100%
52-week high/low (A$)	0.215 / 0.053
Avg. 12M daily volume ('1000)	245.3
Website	www.islandpharmaceuticals.com

Source: Company, Pitt Street Research

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



Source: Refinitiv Eikon, Pitt Street Research

Valuation metrics	
NPV fair valuation range (A$)	0.30-0.40
WACC	15.5%

Source: Pitt Street Research

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Table of Contents

The journey of Island Pharmaceuticals (ASX: ILA) and ISLA-101 to this point

For investors new to the story, we will briefly recap the progress Island Pharmaceuticals (ASX: ILA) has made. ILA's history as a listed company only goes back to 2021, but it was founded a year earlier after a private US company called Isla Pharmaceuticals, that had been working with ISLA-101, was rolled into an Australian incorporated entity with the intention of being listed on the ASX to secure funding for the advancement of ISLA-101.

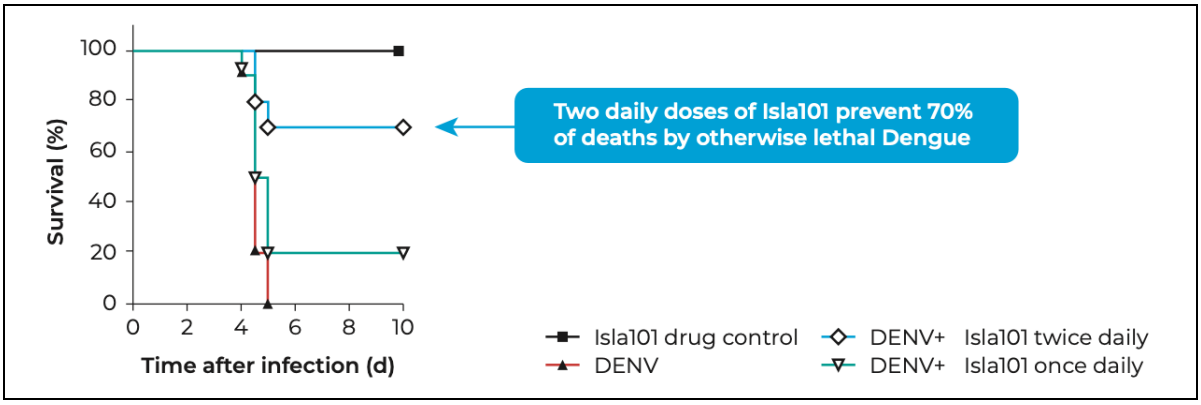
ISLA-101 (or fenretinide) went through ~45 Phase I and II human clinical trials as a therapeutic for cancers and various respiratory illnesses.

ISLA-101 (or fenretinide) is not a new drug, but a repurposed drug. It went through ~45 Phase I and II human clinical trials as a therapeutic for cancers and various respiratory illnesses. The drug was proven safe in all these trials, but efficacy levels were insufficient in any of them to advance to later stages. ISLA-101 was donated to the US National Cancer Institute (NCI) after its developer Johnson & Johnson abandoned development. The program was donated to the US National Cancer Institute (NCI) and it ended up in the hands of Monash University, which is where Island licensed it from.

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 date has 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 (Figure 1 and Figure 2).

ISLA-101 has shown broad spectrum 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[1].

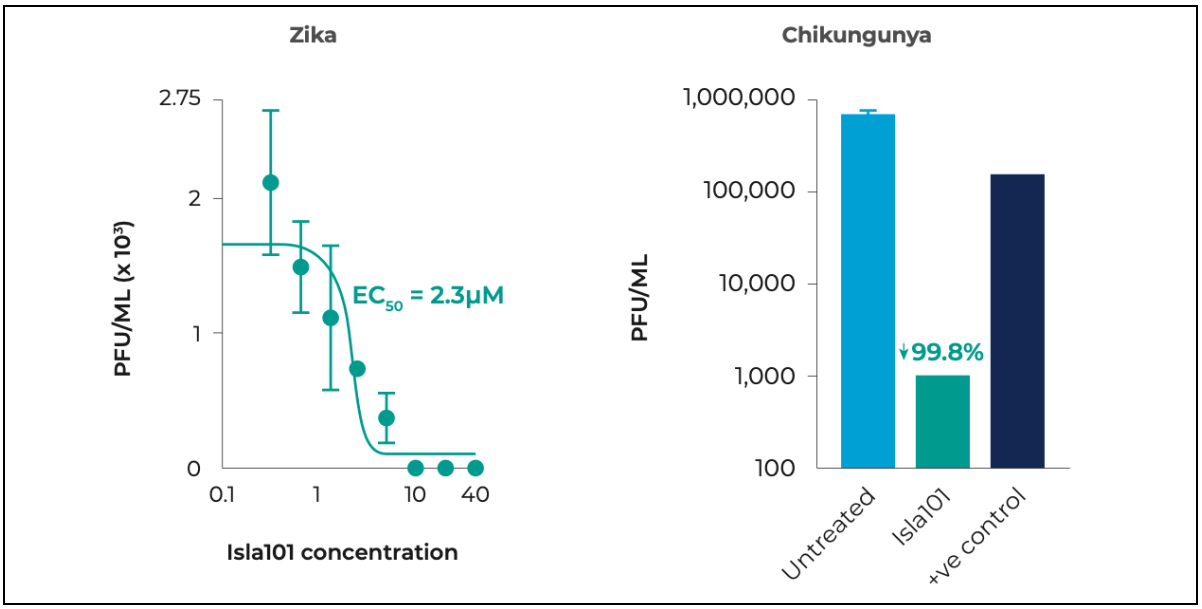
Figure 1: ISLA-101's efficacy against Dengue



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

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

Figure 2: ISLA-101's efficacy against other flaviviruses



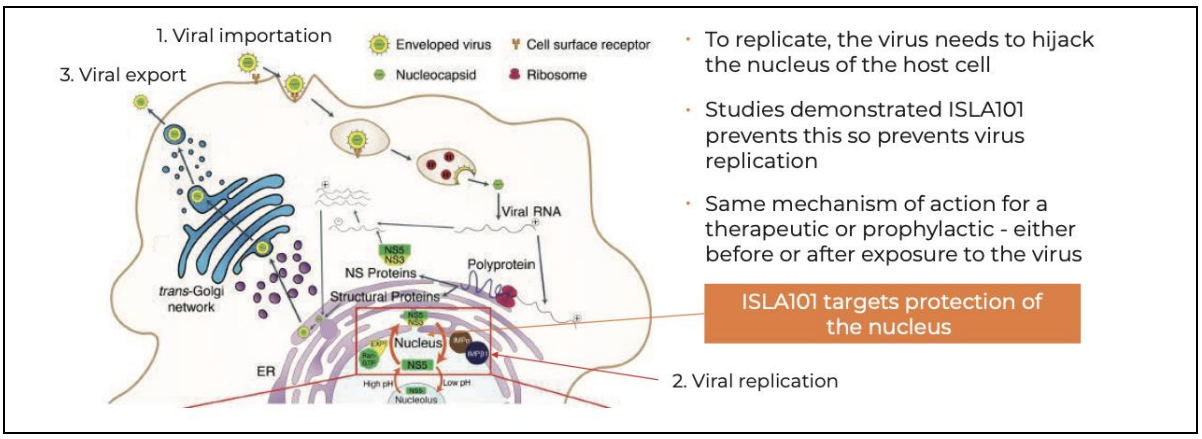
Source: For Zika - Wang et. al. (2017), Nuclear import inhibitor N-(4-hydroxyphenyl) retinamide targets Zika virus (ZIKV) nonstructural protein 5 to inhibit ZIKV infection. Biochem Biophys Res Commun. 2017 Dec 2;493(4):1555-1559. Epub 2017.For Chikungunya: WO 2014/169355.

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 (or spread) of the viral infection (Figure 3).

Figure 3: ISLA-101's Mechanism of Action



Source: Company

The PROTECT trial

The study has distinct arms to show if ISLA-101 could prevent Dengue infection from occurring at all, and to show if it could act as a therapeutic to patients with a live infection.

While it took longer than investors expected for Island to enter Phase 2, the company is just weeks away from unveiling results. The study was renamed PROTECT, short for PROphylactic and TrEatment Challenge Trial, reflecting that the study has both prophylactic and therapeutic arms. In other words, the study had distinct arms to show if ISLA-101 could prevent Dengue infection from occurring at all, and to show if ISLA-101 could act as a therapeutic to patients with a live Dengue infection.

There were 2 phases to the trial each involving a distinct cohort, the first stage (Phase 2a) involved a preventative cohort (healthy individuals exposed to Dengue to see if ISLA-101 could prevent fever) and the second stage (Phase 2b) involved a therapeutic cohort (individuals infected with Dengue and treated with ISLA-101 to see the impact the drug could have, if any). A review of the data from the A cohort was performed in November 2024. A clinical update is expected in April 2025 with unblinded data from the A and B cohort expected before the end of Q2 CY25.

Phase 2a was successful and Phase 2b results are immanent

Results from Phase 2a were successful. The Safety Review Committee (SRC) observed that there had been evidence of antiviral activity in subjects treated with ISLA-101. There were no safety concerns that would necessitate implementing changes to the study. And so, the SRC recommended that the trial proceed to the Phase 2b cohort. The first enrolments occurred in early January 2025 with the balance by the end of that month.

A clinical update from Phase 2b is due in April 2025, with full results from the unblinded data of both cohorts is expected during the June quarter of CY25

Again, we note that results (at least high-level results) are due in April 2025, with full results from the unblinded data of both cohorts is expected during the June quarter of CY25. The results will be determined by examination of subject blood samples for biomarkers of infection, particularly viremia (virus load in the bloodstream).

What will happen when results from PROTECT are released?

Ideally, the results from the second cohort will be positive and the company will continue to move towards commercialisation. It remains to be seen whether a Phase 3 trial would be needed by the FDA for commercialisation. We note that a Phase 3 trial would likely take longer and involve more patients than Phase 2, and the structure of that study is in development. But it is plausible that such a study could be shorter than many other Phase 3 trials on the ASX in recent years because the 'cycle' over which patients are treated is a matter of days rather than months.

Currently, the ISLA-101 program is eligible to receive a Priority Review Voucher (PRV) for ISLA-101 in the event of FDA approval. This will enable ILA to expedite the approval process for another drug or sell that voucher to another company. PRVs can sell for over US$150m – as judged by the most recent PRVs[2]. It goes without saying that such a non-dilutive cash injection would be spectacular for the company.

Of course, worse scenarios are plausible too. This arm of the study could fail, and this would be a setback for the company. Given results from Phase 2a, ILA could try to continue to pursue ISLA-101 as a preventative drug rather

[2] Recent companies to have sold PRVs for >$150m include Zerva Therapeutics (in February 2025), Acadia Therapeutics (in November 2024) and PTC Therapeutics (in November 2024).

than a therapeutic drug, although it remains to be seen if this would be pursued.

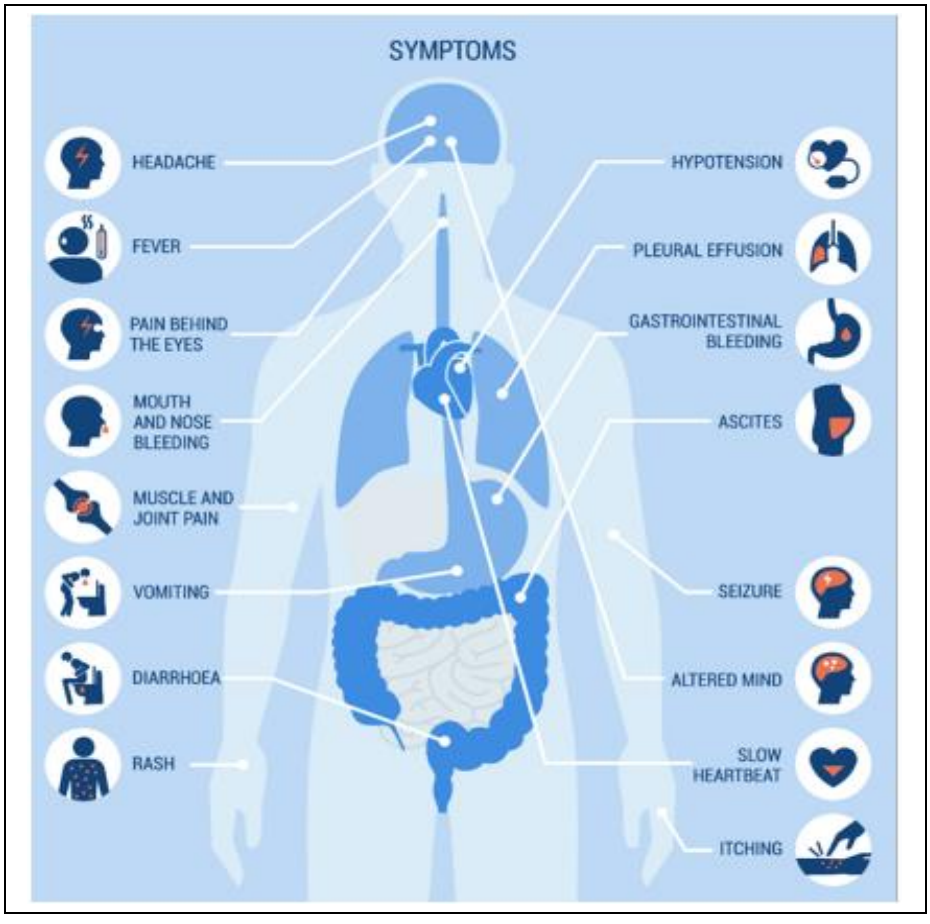
It is also possible that the data may be positive, but the data or the submission may not be acceptable to regulators such as the FDA. It may order the company to conduct another trial or ask for further clarification in the form of a Complete Response Letter (CRL). As the recent case study of Cyclopharm (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, such as labelling issues or manufacturing concerns.

There's a need for Dengue solutions, and ILA might be able to help

Dengue infections occur as a result of mosquito bite by a mosquito infected with the virus, and symptoms develop within 3-14 days.

Dengue (pronounced 'deng-gey') is a flavivirus – a virus transmitted by mosquitos. Dengue affects infants, children and adults with symptoms developing between 3 and 14 days of a mosquito bite. 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 contact (unless blood is involved). Symptoms including headaches, gastrointestinal bleeding, a reduction in blood platelets, seizures, itching, rashes and vomiting (Figure 4).

Figure 4: Dengue symptoms



Source: Company

Over 14 million people were infected by Dengue in 2024 and over 100,000 in January 2025 alone.

Dengue is a major societal problem, being endemic in over 100 countries and infecting millions annually – it is estimated that over 14 million people were infected in 2024 and over 100,000 in January 2025 alone[3]. What is concerning is that while Dengue has long been confined to tropical countries with ideal 'breeding ground' for mosquitos, it is cropping up in countries where you wouldn't expect the disease to occur. For instance, there were locally acquired cases in France, Italy and Spain last year.

The incidence is expected to increase because of climate change and increasing urbanisation. The Rockefeller Foundation estimates that Dengue will impact 60% of the world's population by 2080[4]. 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.

There are few treatment 'options'

There are no direct treatments for Dengue, only treatments that aid specific symptoms.

As we've outlined in previous notes on ILA, there are no direct treatments, only treatments that aid specific symptoms (such as fever), but do not fight the disease itself. In the US, hospitalisation tends to cost US$7,000 per patient.

If ISLA-101 can fight Dengue infections and/or act as a preventative mechanism, it could have a market practically all to itself and would make a significant difference in all the patients Island Pharmaceuticals (along with its future commercial partners) could reach.

ISLA-101 could target other flaviviruses too

While Dengue is the most prominent flavivirus which Island Pharmaceuticals is targeting, and the indication where the company is most advanced, it is plausible that the company could target other flaviviruses in the future. And 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.

The most prominent of these is Zika, which has a lower spread than Dengue, but has occasional outbreaks (particularly during 2015-16). Then there's Yellow Fever for which vaccines exist but there are only symptomatic treatments. The receipt of a Yellow Fever vaccine is commonly a travel requirement for visitors travelling to or from endemic countries. Others include the West Nile Virus, Chikungunya virus and is Japanese encephalitis virus (JEV).

[3] https://www.ecdc.europa.eu/en/Dengue-monthly
[4] https://www.rockefellerfoundation.org/insights/perspective/the-increasing-burden-of-Dengue-fever-in-a-changing-climate/

Our Valuation of Island Pharmaceuticals

We derived a value of A$83.0m in our base case and A$109.1m in our bull case, or $0.30 per share and $0.40 per share.

We reiterate our valuation Island Pharmaceuticals as outlined in our initiation report A$83.0m in our base case and A$109.1m in our bull case. Under the current number of shares on issue, these amount to is $0.30 per share and $0.40 per share respectively (Figure 5). Investors interested in a full outline of our model inputs should see our initiation report, but they are briefly recapped in Figure 6). These assume that Island passes Phase 2 (the PROTECT trial) then commences Phase 3 within 12 months from now, using a licensing model, then obtains FDA approval in mid-FY28 and has a 7-year period of market exclusivity.

Figure 5: 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: Pitt Street Research

Figure 6: Our valuation of 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)	276,061,285	276,061,285
Implied price	**$ 0.301**	**$ 0.395**
Current share price	$ 0.165	$ 0.165
Premium	*82%*	*140%*

Source: Pitt Street Research

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**. Notwithstanding this risk has been significantly diminished with the recent placement and the prospect that Island could obtain a PRV, the prospect of Island needing debt or equity sources of funding cannot be entirely ruled out. In such an event, 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.

Appendix I – 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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