Date
09 December 2021

Theme
Initiating Coverage

Company
Hexima Limited (HXL)

WILSONS Equity Research

New O/W: Break on through to the other side

We initiate coverage on Hexima with an OVERWEIGHT rating and a risked price target of $0.75 per share. Hexima has been reborn as an ASX-listed entity. This iteration explores the pharmaceutical value of plant-derived, antifungal 'defensin' biology, having abandoned earlier agricultural pursuits in crop protection. Its lead asset pezadeftide has achieved promising early clinical results treating deep seated fungal infections of the toenail (onychomycosis) as a topical medication. Pezadeftide is a water-soluble agent that penetrates nails rapidly, devastates the fungal pathogens in the nail bed and allows healthy nail regrowth. Our thesis is that the availability of an efficacious, pragmatically priced, short-course treatment option can create a mini-blockbuster in dermatology. We assess US$365M peak sales in US and Japan. Pezadeftide's novel mechanism of action makes it a logical candidate for investigation in other poorly served anti-fungal markets.

Recommendation	OVERWEIGHT
12-mth target price (AUD)	$0.75
Share price @ 08-Dec-21 (AUD)	$0.35
Forecast 12-mth capital return	114.3%
Forecast 12-mth dividend yield	0.0%
12-mth total shareholder return	114.3%
Market cap	$51m
Enterprise value	$48m
Shares on issue	147m
Sold short	
ASX 300 weight	n/a
Median turnover/day	$0.0m

Dr Shane Storey
shane.storey@wilsonsadvisory.com.au
Tel. +61 7 3212 1351

Dr Melissa Benson
melissa.benson@wilsonsadvisory.com.au
Tel. +61 2 8247 6639

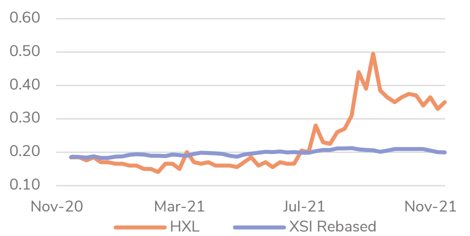
Key points

Introducing Hexima Limited. Hexima originally listed in 2007 as a plant genetics company with plans to commercialise anti-fungal and other traits for crop protection. After a delisted hiatus period Hexima's 'defensin' IP finds new life in pezadeftide. This novel, anti-fungal peptide has achieved promising results in a Phase I/IIA clinical trial treating onychomycosis: demonstrating high rates of toenail penetrance, potent fungicidal activity and nearly twice the rate of mycological cure at 12 weeks compared to existing options. Hexima has enrolled a Phase IIB to confirm these results and investigate treatment periods as short as 12 weeks (noting all approved topical medications are labelled for 48 weeks of daily dosing). Hexima is planning a Phase III program to commence in 2022.

Onychomycosis market forecast. Our target net sales projection for pezadeftide is US$250M in the US market with upside >US$350M depending on efficacy, pricing and market access tactics. In the US, pezadeftide could launch into an uncontested branded market with today's leader JUBLIA facing generic competition from 2026. A sensibly priced, short-course topical treatment should also readily displace low-efficacy, generic prescription-only and OTC topical treatments that patients resort to.

Valuation. Our fully diluted $0.75 price target combines real options analyses of: a) independent commercialisation in the US market; and b) Pharma licensing scenarios to access the Japanese market. Our un-risked valuation is $2.48 per share before investigating: a) the propensity for elevated market growth given the availability of an easier/cheaper treatment option; and b) indication expansion into superficial infections.

12-mth price performance ($)



	1-mth	6-mth	12-mth
Abs return (%)	-5.4	125.8	89.2
Rel return (%)	0.1	125.4	81.7

Risks and catalysts

Risks: a) clinical trial failures; b) access to development capital; c) uncertain valuation inputs (sales forecasts). **Catalysts**: a) clinical trial success; b) corporate activity including licensing and M&A.

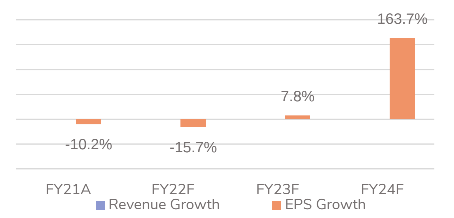
Earnings forecasts

Year-end June (AUD)	FY22A	FY23F	FY24F	FY25F	FY26F
NPAT rep ($m)	-9.3	-15.2	9.7	-49.8	-24.6
NPAT norm ($m)	-9.3	-15.2	9.7	-49.8	-24.6
Consensus NPAT ($m)					
EPS norm (cps)	-7.1	-6.5	4.2	-21.4	-10.6
EPS growth (%)	-15.7	7.8	163.7	-614.0	50.7
P/E norm (x)	-4.9	-5.3	8.4	-1.6	-3.3
EV/EBITDA (x)	-5.3	-3.2	4.8	-1.0	-2.0
FCF yield (%)	-19.0	-19.6	22.6	-94.9	-29.0
DPS (cps)	0.0	0.0	0.0	0.0	0.0
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0
Franking (%)	0	0	0	0	0

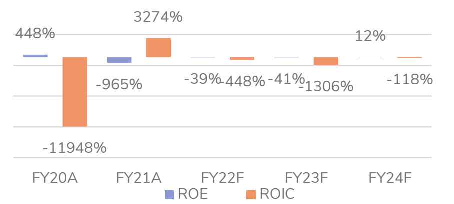
Source: Company data, Wilsons estimates, Refinitiv

Wilsons Equity Research
Wilsons restricts research analysts from trading in securities for which they write research. Other Wilsons employees may hold interests in the company, but none of those interests are material. Wilsons further advises that at the date of this report, neither Wilsons Advisory and Stockbroking Limited or Wilsons Corporate Finance Limited have any material interests in the company.

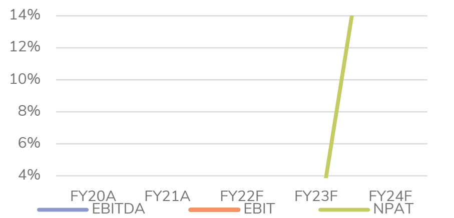
Growth rates



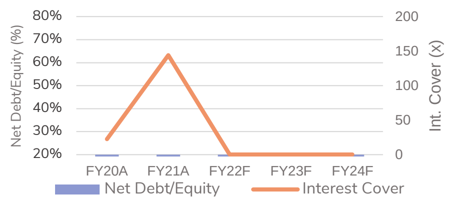
Returns



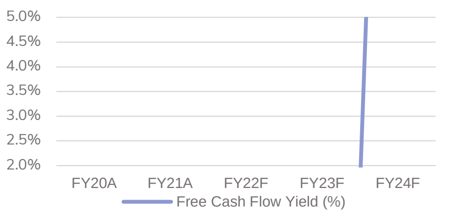
Margin trends



Solvency



Free cash flow yield



Interims ($m)

	1H21A	2H21A	1H22E	2H22E
Sales revenue	0.0	0.0	0.0	0.0
EBITDA	-2.7	-4.0	-4.0	-5.0
EBIT	-2.8	-4.1	-4.1	-5.2
Net profit	**-2.7**	**-4.1**	**-4.1**	**-5.2**
Norm EPS	**-2.9**	**-3.2**	**-3.1**	**-4.0**
EBIT/sales (%)				
Dividend (c)	0.0	0.0	0.0	0.0
Franking (%)	0.0	0.0	0.0	0.0
Payout ratio (%)	0.0	0.0	0.0	0.0
Adj payout (%)	0.0	0.0	0.0	0.0

Key assumptions

	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F	FY28F	FY29F
Revenue Growth (%)	-100.0	0.0	0.0	0.0	0.0	-2.8	-100.0	30.3
EBIT Growth (%)	34.4	63.5	-163.7	-614.0	-50.7	32.6	-139.8	-151.4
NPAT Growth (%)	35.3	63.5	-163.7	-614.0	-50.7	72.4	-139.8	-151.4
EPS Growth (%)	**15.7**	**-7.8**	**-163.7**	**-614.0**	**-50.7**	**72.4**	**-139.8**	**-151.4**
EBIT / Sales (%)	0.0	0.0	0.0	0.0	-52.2	-71.2	12.9	-5.1
ROA (%)	**-19.6**	**-40.2**	**6.6**	**-50.7**	**-31.4**	**-75.4**	**25.9**	**-14.0**
ROE (%)	**-20.8**	**-52.1**	**7.6**	**-63.1**	**-45.4**	**-136.6**	**42.4**	**-24.9**

Financial ratios

	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F	FY28F	FY29F
PE (x)	-4.9	-5.3	8.4	-1.6	-3.3	-1.9	4.8	-9.4
EV/EBITDA (x)	-5.3	-3.2	4.8	-1.0	-2.0	-1.5	3.6	-7.5
Dividend yield (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FCF yield (%)	-19.0	-19.6	22.6	-94.9	-29.0	-42.4	11.8	-8.6
Payout ratio (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Adj payout (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Profit and loss ($m)

	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F	FY28F	FY29F
Sales revenue	0.0	0.0	33.3	0.0	47.1	45.8	100.1	130.5
EBITDA	-9.0	-14.9	10.0	-49.5	-24.3	-32.3	13.3	-6.4
Depn & amort	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
EBIT	**-9.3**	**-15.2**	**9.7**	**-49.8**	**-24.6**	**-32.6**	**13.0**	**-6.7**
Net interest expense	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	0.0	0.0	0.0	0.0	0.0	9.8	-3.9	2.0
Minorities/pref divs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Equity accounted NPAT	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (pre-sig items)	**-9.3**	**-15.2**	**9.7**	**-49.8**	**-24.6**	**-42.3**	**16.8**	**-8.6**
Abns/exts/signif	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reported net profit	**-9.3**	**-15.2**	**9.7**	**-49.8**	**-24.6**	**-42.3**	**16.8**	**-8.6**

Cash flow ($m)

	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F	FY28F	FY29F
EBITDA	-9.0	-14.9	10.0	-49.5	-24.3	-32.3	13.3	-6.4
Interest & tax	0.0	0.0	0.0	0.0	0.0	9.8	-3.9	2.0
Working cap/other	-0.8	4.9	1.6	0.8	9.4	0.8	-3.3	0.0
Operating cash flow	**-9.8**	**-10.0**	**11.6**	**-48.7**	**-14.9**	**-21.7**	**6.0**	**-4.4**
Maintenance capex	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Free cash flow	**-9.8**	**-10.0**	**11.6**	**-48.7**	**-14.9**	**-21.7**	**6.0**	**-4.4**
Dividends paid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Growth capex	-0.6	-0.6	-0.6	-0.6	-0.6	-0.6	-0.6	-0.6
Invest/disposals	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Oth investing/finance flows	-2.0	0.0	-4.0	0.0	0.0	0.0	0.0	0.0
Cash flow pre-financing	**-12.4**	**-10.6**	**7.0**	**-49.3**	**-15.5**	**-22.3**	**5.4**	**-5.0**
Funded by equity	50.5	0.0	100.0	0.0	0.0	0.0	0.0	0.0
Funded by debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Funded by cash	-38.1	10.7	-107.0	49.3	15.5	22.4	-5.4	5.0

Balance sheet summary ($m)

	FY22F	FY23F	FY24F	FY25F	FY26F	FY27F	FY28F	FY29F
Cash	41.5	30.8	137.8	88.5	73.0	50.6	56.1	51.1
Current receivables	4.5	5.3	6.4	7.3	2.6	2.5	5.5	7.2
Current inventories	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.2
Net PPE	0.4	0.7	1.0	1.3	1.6	1.9	2.2	2.5
Intangibles/capitalised	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total assets	**47.4**	**37.8**	**146.2**	**98.1**	**78.2**	**56.1**	**64.9**	**61.9**
Current payables	1.0	7.0	10.0	12.0	17.0	18.0	18.0	20.0
Total debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total liabilities	**2.7**	**8.6**	**18.3**	**19.1**	**24.1**	**25.1**	**25.1**	**27.1**
Shareholder equity	**44.7**	**29.2**	**127.9**	**79.0**	**54.1**	**31.0**	**39.8**	**34.8**
Total funds employed	**44.7**	**29.2**	**127.9**	**79.0**	**54.1**	**31.0**	**39.8**	**34.8**

Table of Contents

Glossary

Azole	Azoles are a class of drug featuring a 5-membered cyclic ring structure. A multitude of azoles have been developed with anti-fungal activity including efinaconazole, fluconazole, itraconazole, posaconazole, vorinconazole and ravuconazole.
BLA	A Biologics License Application (BLA) is a type of FDA drug submission required to grant marketing authorisation for drugs that are biologic in nature, i.e. Antibody or protein-based drugs, such as pezadeftide.
Ciclopirox	Ciclopirox is a synthetic antifungal agent. A topical formulation PENLAC (8% solution) is indicated for onychomycosis. Ciclopirox creams, gels, shampoos and other formulations are available for other superficial fungal infections.
Clinical efficacy	Clinical efficacy is a secondary endpoint in onychomycosis trials that monitors the percentage area of target nail that has been cleared of infection on a visual basis. By difference, the percentage of diseased nail surface area can be calculated. Thresholds differ but ≤10% involvement is a widely reported benchmark.
Complete cure	Complete cure is often the primary endpoint in onychomycosis trials. For a complete cure the target nail must have both a mycological cure AND have zero residual, visible infection.
Dermatophyte	Dermatophytes are a common group of fungi that commonly causes diseases of the skin and nails in humans. Traditionally, this term includes species of *Microsporum*, *Epidermophyton* and *Trichophyton*. Common clinical presentations include onychomycosis, tinea and ringworm.
Efinaconazole	Efinaconazole is an anti-fungal molecule discovered by Kaken Pharmaceutical and indicated for the topical treatment of onychomycosis. It is a member of the azole class of anti-fungal drugs. The molecule is available as JUBLIA in North American markets and as CLENAFIN in Japan. In July 2021 Almirall signed to commercialise efinaconazole in Europe.
FDA	The Food and Drug Administration (FDA) is responsible for regulation and approval of food and therapeutic medicines used within the USA.
Mycological cure	Mycological cure is a popular secondary endpoint in onychomycosis trials. To register a mycological cure the target nail must be negative on both KOH microscopy and attempts to culture fungal growth from samples (clippings etc).
Non-dermatophyte mould	Non-dermatophyte moulds are another class of fungi implicated in the aetiology of onychomycosis. Species including *Scopulariopsis spp.* and *Aspergillus spp.* can cause onychomycosis themselves or be present as coinfections with more common dermatophyte fungi.
Onychomycosis	Onychomycosis (tinea unguium) is a fungal infection of the nail bed, matrix or nail plate. Onychomycosis accounts for one half of all nail disease and occurs primarily in adults aged 60 or more years. The disease is difficult to treat on account of the nail bed providing a protective environment for the fungi, ineffective therapies and high rates of re-infection and recurrence.
Pezadeftide	Pezadeftide is an antimicrobial peptide based on a naturally occurring defensin from Florida bitterbush (*Picramnia pentandra*). The drug molecule is Hexima's lead asset.
Pharmacy Benefits Manager (PBM)	In the US healthcare system, PBMs are third-party administrators that manage pharmaceutical benefits on behalf of public and private health insurance plans. After much industry consolidation over the last decade three PBMs control ~80% of US insured lives (Express Scripts, CVS and UnitedHealth).
PMDA	Pharmaceuticals and Medical Devices Agency is a Japanese government organisation with similar functions to the US FDA.
Prior Authorisation (PA)	In the US healthcare system, prior authorisation can be a prerequisite for the cost of the drug or therapy being reimbursed by a patient's health insurer.
Step Edits	In the US healthcare system, step-edits are a form of controlling access to expensive medicines. Patients are required to try drugs in ascending order of cost. Lower cost alternatives may include generic versions of the drug originally prescribed or other medicines approved for the same indication.
Tavaborole	Tavaborole is a protein synthesis inhibitor originally developed by Anacor but now marketed in the US by Sandoz (Novartis) as KERYDIN. Sandoz paid Almirall US$65M in initial upfronts and milestones plus a profit share.

1. Investment thesis

We initiate coverage on Hexima with an OVERWEIGHT rating and a risked price target of $0.75 per share. Hexima has been reborn as an ASX-listed entity. This iteration explores the pharmaceutical value of plant-derived, antifungal 'defensin' IP, having abandoned earlier agricultural pursuits in crop protection. Lead asset pezadeftide has achieved promising early clinical results treating deep seated fungal infections of the toenail (onychomycosis) as a topical medication. Pezadeftide is a water-soluble agent that penetrates nails rapidly, devastates the fungal pathogens in the nail bed and allows healthy nail regrowth. Our thesis is that the availability of an efficacious, pragmatically priced, short-course treatment option can create a mini-blockbuster in the US dermatology/podiatry market. Pezadeftide's novel mechanism of action makes it a logical candidate for investigation in other poorly served, superficial anti-fungal settings including cutaneous aspergillosis and candidiasis.

1.1 Investment merits

Elegant solution to an intractable problem in dermatology/podiatry. The structure of pezadeftide is based on a class of plant host-defence peptides called defensins. Pezadeftide is a hydrophilic antimicrobial peptide whose solubility allows it to pass readily through human toenails to reach the source of infection in the nail bed. Pre-clinical work demonstrates good distribution across, and accumulation of drug within the nails, resulting in materially higher rates of drug penetration. The drug is lethal to fungal cells with a mechanism of action unlikely to prompt the development of drug-resistance.

A short treatment course can change the treatment of onychomycosis. The standard of care for onychomycosis is either the oral or topical administration of anti-fungal drugs. Oral drugs have the highest intrinsic efficacy (~30% cure rates on an intent-to-treat basis) but are unpopular due to side effects and drug-drug interactions. Topical drugs are safer but require long treatment (48 weeks versus 12 weeks) with lower success rates (4%-17%). Hexima's program is targeting a 12-36 week topical treatment course after achieving a 69% mycological cure after 6 weeks of daily treatment. We assess this product specification would displace incumbent branded topical medications, low cost generics and the multitude of OTC concoctions available for onychomycosis.

An un-contested, high value branded drug market could await in 2026. Bausch Health Care's JUBLIA has led the branded topical market since launch in 2014. Generic competition is expected to erode JUBLIA from 2026, the same year we expect FDA may approve pezadeftide. Pezadeftide is the only new chemical entity we can see heading towards Phase III development. If Bausch stops promoting JUBLIA in response to generics, pezadeftide will face very limited competition.

Clear clinical pathway. Hexima is conducting a Phase IIB trial evaluating three dosing strategies. Results are expected in 2Q 2022 enabling the start of a Phase III campaign towards the end of CY22. Previously approved topical drugs have established trial design predicates for Hexima to follow. We expect two Phase III trials assessing complete cure at 52 weeks as the primary endpoint.

Long-dated patent protection. Hexima is protected by granted patents in the USA, Europe, Japan and China with expiry dates 2035-2036. As a biologic entity, pezadeftide may also be eligible for 12 years' exclusivity under the Patient Protection and Affordable Care Act. In future, Hexima may pursue paediatric studies to secure an additional six months of patent term exclusivity.

Indication expansion and novel formulations. Pezadeftide and/or other defensin species owned by Hexima may be developable for other settings where fungal infections are poorly managed. Given the fungistatic rather than fungicidal nature of most available drug classes (azoles, polyenes, echinocandins) drug resistance is common. Pezadeftide's activity against *Candida* encourages prospects in cutaneous and possibly vulvovaginal candidiasis.

Immense product and valuation upside. Hexima is deeply undervalued at this time with a relatively low profile, having only been re-admitted to ASX in November 2020. Our un-risked valuation of $2.48 share is a 12-month forward valuation. Peak US sales estimate is the primary driver of valuation. Our base case is US$250M but sensitivity and scenario analyses explore upside to US$500M.

1.2 Important risks

Clinical trial and regulatory risk. As with any clinical development stage biopharmaceutical company, there are inherent investment risks associated with the outcomes of clinical trials and subsequent regulatory marketing authorisation decisions. Investment decisions rely on analysis of publicly disclosed non-clinical and Phase I/II data, much of which is yet to be published in a peer reviewed forum. Although Hexima's clinical studies are small, their blinded, randomised, vehicle-controlled design allows some confidence in the preliminary efficacy signals. Comparative benchmarking analyses helps contextualise those results but ultimately rests on inherently flawed cross trial comparisons against other approved and investigational onychomycosis agents. Well designed, adequately powered and perfectly executed clinical trials can still fail to deliver the desired outcome. Biotechnology companies that experience adverse clinical trial results are subsequently valued at or below their available cash reserves.

Technology and competitive risks. To the best of our research efforts, pezadeftide is the only new chemical or biological entity at Phase IIB clinical trial stage with nothing ahead of it in Phase III development. Our searches are limited to publicly available clinical literature, patent filings and clinical trial registries and are therefore incomplete.

Market structure is difficult to predict. The onychomycosis market is different in every major jurisdiction. In the USA, the market is fragmented and complicated by OTC and off-label factors for which visibility is poor. We have controlled for this by basing our market model on observable prescribing activity limited to branded and generic drugs. We suspect the pool of patients seeking treatment is materially larger than what we have assumed.

Intellectual property risk. Hexima's key patent families are reviewed in Appendix A3. The portfolio offers both 'composition of matter' and 'method of use' forms of protection extending to at least 2035 on a statutory basis. As with any pharmaceutical asset, the pezadeftide patents are open to challenge at any time by competitors seeking to invalidate them. Note that as a biologic drug, pezadeftide is eligible for 12 years of market exclusivity, independent of patent protection, from the date of FDA approval. We have not conducted any explicit analysis of patent validity or freedom to operate.

Financial risk. As with most pre-commercialisation biotech companies, Hexima requires continued capital investment to support its clinical development programs with no revenues to support these costs for at least 4-5 years. Lack of available capital to fund clinical development programs and/or commercialisation of their assets is a risk given the changes in market conditions that may occur which could be unfavourable with regards to capital availability.

Valuation risk in the absence of catalysts. Our SOTP valuation is premised on successful clinical and commercial development of pezadeftide. The real-options methodology we have used depends ultimately on the quality of the sales projections we have prepared and reference in Section 3.3. Computing 'risked' valuations requires the assignment of success probabilities, predicated on subjective judgement and experience and therefore open to error.

2. Valuation

2.1 Price target $0.75 (risked)

We have used a sum of the parts (SOTP) approach to value Hexima with a focus on pezadeftide commercialisation in the USA and Japan. We explore label expansion opportunities into paediatric and other high-risk populations by way of sensitivities.

Our initiating SOTP valuation comprises:

- Real options analysis of independent commercialisation of pezadeftide in the USA from FY26e launch;
- Real options analysis of an exclusive licensing transaction with a Japanese Pharma under which Hexima stands to receive milestone and royalty payments.

At this point in time we have not attributed any value to pezadeftide's potential in other indications. The reasoning behind exclusion of these pipeline programs is due to the early degree of progression and lack of development capital. Our risked valuation of $0.75 per share is attenuated by certain risk probabilities in relation to clinical trials, regulatory approvals and market access assumptions. Setting these probabilities to 100% provides an estimate of $2.48 per share on a fully diluted basis.

Table 1. Sum-of-the-parts (SOTP) valuation for Hexima only considers US and Japanese rights to pezadeftide for the treatment of onychomycosis.

Valuation component	Risked valuation (A$M)	Comments	Unrisked valuation (A$M)
US pezadeftide commercialisation	127.7	Real options analysis on FY26 independent product launch	443.6
JP partnering optionality	40.2	Real options analysis of FY24 exlusive licensing transaction	114.2
Equity value (A$M)	167.9		557.8
Price target (A$/share)	**0.75**		**2.48**

Source: Wilsons

2.2 Valuation of independent commercialisation option in the USA

The underlying revenue and earnings model for this part of our valuation is provided in Section 3.3.1. Briefly, we model US peak net sales of US$250M which assumes 30% share of the prescription market with no explicit assumptions about onychomycosis market expansion.

Key results:

- We assess a project NPV of $716.9M as at the point of FY26e launch;
- Value is modelled over four inflection points: a) Phase IIB success; b) Phase III success; c) FDA approval; and d) market access outcomes (reimbursement and pricing outcomes at least as favourable as our model assumptions). The expected timing of these inflection milestones is provided in Table 2 below.
- We have assumed $35M in development costs specific to development in this jurisdiction.
- We assess the present value of this option as $127.7M.
- Un-risked present value of the option is $444M or $1.97 per share.

Table 2. Real-options framework for US commercialisation.

pezadeftide - USA	Phase IIB	Phase III	FDA approval	Market Access
Estimated probabilities (p)	70%	65%	85%	85%
Estimated timing	1/03/2022	30/12/2024	30/12/2025	23/02/2026
R&D costs (A$m)	-	20.0	10.0	5.0
S+ (upside values, A$m)	223.9	451.4	584.2	697.2
S- (salvage values)	-	-	-	-
S (start of phase value)	153.1	223.9	451.4	584.2
Real option values (A$m)	**134.8**	**197.0**	**437.5**	**579.2**

Source: Wilsons

Source: Wilsons

2.3 Valuation of Japanese partnering scenario

The underlying revenue and earnings model for this part of our valuation is provided in **Section 3.3.2** Briefly, we model Japanese peak net sales of approximately US$115M.

Key results:

- We assess a project NPV of $172.9M.
- Licensing transaction settled in 2024 after positive Phase III trial results with milestone payments up to US$150M plus royalties (low double-digit percentage of net sales).
- In NPV terms, Hexima's royalties and milestone payments are weighted 45:55.
- In NPV terms, Hexima's share of overall asset cash flows is 42%.
- We have assumed zero development costs specific to development in this jurisdiction (expecting a Japanese partner to sponsor any bridging studies to secure PDMA approval).
- We assess the present value of this option as $40.2M on the basis that trial outcomes, timing and partnering terms are as good or better than our scenario assumptions.
- Un-risked present value of the option is $114M or $0.51 per share.

Table 3. Real-options framework for Japanese partnering option.

pezadeftide - Japanese partnering	Phase IIB	Partnering	PDMA approval	Market Access
Estimated probabilities (p)	70%	75%	85%	79%
Estimated timing	1/03/2022	30/12/2024	30/12/2025	23/02/2026
R&D costs (A$m)	-	-	-	-
S+ (upside values, A$m)	59.6	104.2	134.8	172.9
S- (salvage values)	-	-	-	-
S (start of phase value)	40.8	59.6	104.2	134.8
Real option values (A$m)	**40.8**	**59.6**	**104.2**	**134.8**

Source: Wilsons

2.4 Valuation sensitivities

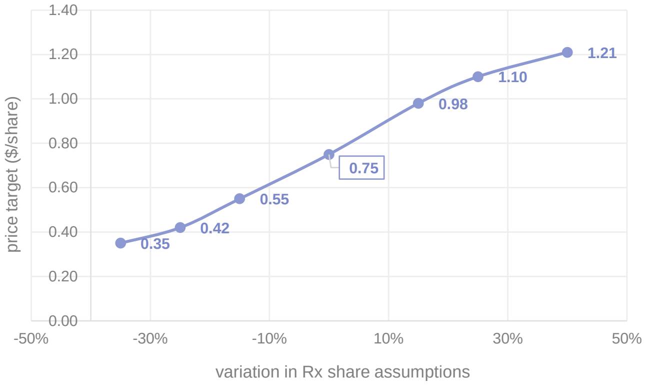
We assess the primary drivers to valuation sensitivity are related to factors affecting peak sales estimates including market share and pricing. Pezadeftide's propensity to grow the topical prescription category is also a potential driver of valuation. In Table 4 we summarise the results of sensitivity analyses and scenario modelling we performed around our base case US peak sales estimate of US$250M.

Table 4. Drivers of valuation sensitivity

Sensitivity	Assumption (*deviation from base case*)	US peak sales range	Δ PT	Revised PT range
Market share	± 15% and ±25% relative differences in assumed maximum market penetration in US market segments. Valuation implications are a linear function of market share (assumes fixed base case ASP and gross margin). See **Figure 1**.	US$211M to US$285M @ ±15% US$185M to US$310M @ ±25%	-27% to +31% @ ±15% -44% to +47% @ ± 30%	$0.55- $0.98 $0.42 - $1.10
Pricing	Analysis examined the range US$200 to US$500 as a net price per prescription. In scenario modelling the obvious gross margin and fixed cost leverage are likely offset at higher prices by market access restrictions. In our scenarios we assess an optimum price of ~US$370 per unit. At US$500 per prescription we assess lower net sales and valuation. See **Figure 2**.	US$165M to US$315M	-61% to +43%	$0.29 @US$200 $1.07 @US$400
Treatment compliance	Variation in the average treatment compliance from 50% to 100% (or in pezadeftide treatment course terms 1.5-3.0 bottles per patient. Our base case is 2 bottles per patient. See **Figure 3**.	US$186M to US$372M	-44% to +87%	$0.42 to $1.40
Category expansion	Our base case assumes only 2% annual growth in the topical Rx category after the launch of pezadeftide. Scenario analysis tested growth rates of 0% to 7.5%. We assess that higher rates of growth are possible if the efficacy of pezadeftide attracts more OTC patients into the Rx category. The topical market could expand by another 40-50%. See **Figure 4**.	Up to US$375M	Up to +93%	Up to $1.45
Jurisdiction extensions	Our assessment suggests that Europe is mainly an OTC market and is discounted in our model and valuation. Canada appears to be an attractive market with >US$40M in annual JUBLIA sales. Modest opportunities exist in Australia, and New Zealand (A$10M sales markets). Hexima has granted patents in China but we have not conducted any assessment of that market.	Up to US$350M adding Canada, Australia and New Zealand	Up to +71%	Up to $1.29
Indication expansion (superficial)	We estimate that the superficial fungal infection market is a ~US$1B net sales market comprising onychomycosis and numerous skin infections.	>US$500M	>100%	n/a

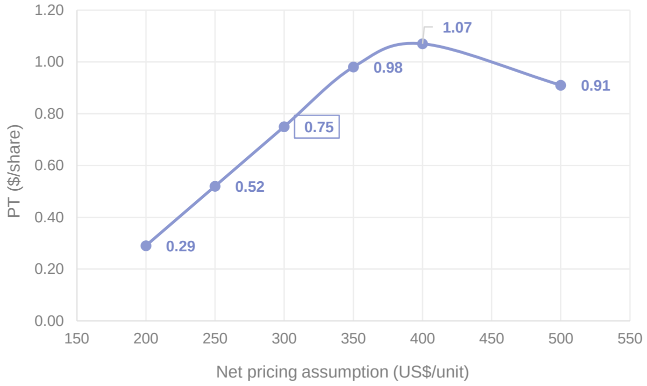
Source: Wilsons

Figure 1. PT sensitivity to variation in market share assumptions.



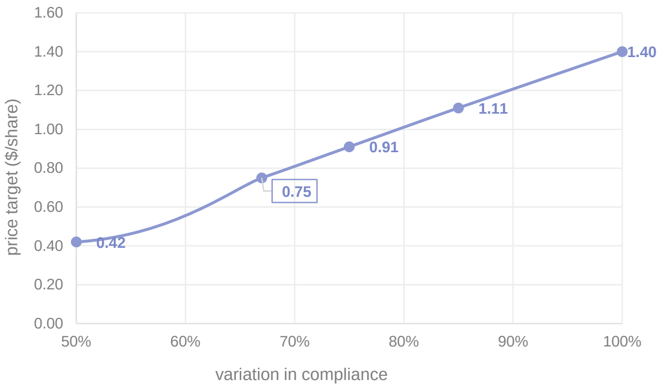
Source: Wilsons

Figure 2. PT sensitivity to unit pricing scenarios.



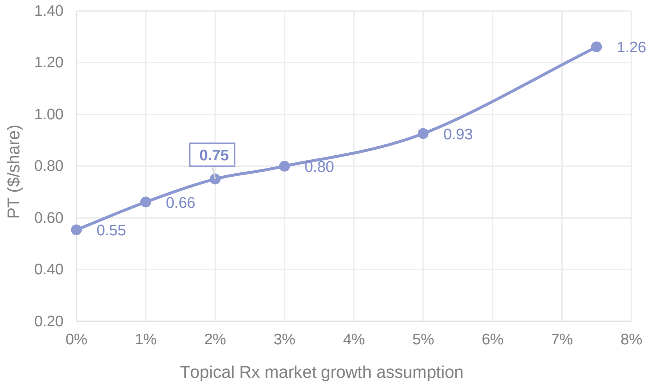
Source: Wilsons

Figure 3. PT sensitivity to variation in treatment compliance assumptions.



Source: Wilsons

Figure 4. PT sensitivity to topical Rx market growth assumptions.



Source: Wilsons

3. Forecasts

Hexima's commercialisation plans for pezadeftide are subject to securing regulatory approvals in the major markets. Our revenue and earnings forecasts are predicated on Hexima pursuing a mix of direct sales and out-licensing models to commercialise pezadeftide. We adopt a direct sales model for the US. For the Japanese market we model a development partner in-licensing Hexima's intellectual property. Under such arrangements, a potential licensor (Pharma) would seek exclusive rights to commercialise pezadeftide. Hexima would expect to receive upfront fees and other milestone payments linked to clinical trial success, regulatory clearances, PMDA approval and cumulative product sales targets. Royalty arrangements are also customary.

3.1 US onychomycosis Rx market model

3.1.1 Treatment pathways

Clinical practice in onychomycosis is relatively static without any major change in clinical guidelines since 2014[1]. Our research suggests that the treatment pathway in the US moves through up to three phases in ascending order of treatment costs.

- Over the counter topical products. This non-prescription segment of the market reflects approximately 1.1M patients annually but is difficult to characterise, owing to a lack of data. OTC topical and/or 'natural' preparations include a range of 'actives' including tolnaftate, tea tree oil, coniferous lacquers, cough suppressants, plant extracts and ozonised sunflower oil[2]. These are low-cost alternatives based on limited anti-fungal activity. Tolnaftate deserves special mention as it is commercialised more broadly by Tetra Corporation in the USA with a range of formulations, some of them proprietary. Tetra's Formula-3 and Formula-7 anti-fungal formulations are sold to primary care physicians and podiatrists who on-sell to patients (Figure 5). Tetra's marketing materials are highly suggestive of onychomycosis, whilst only claiming to be effective for athlete's foot and ringworm.
- Generic, prescription-only medications.
    a) Oral generics tend to be offered first as they are associated with the highest complete cure rates of all approved agents. This category is thoroughly genericised with leading brands SPORONOX[3] (itraconazole) and LAMISIL[4] (terbinafine), both off patent. Itraconazole dosed at 200mg/day for three months is associated with a 52±9% cure rate[5]. Oral terbinafine dosed at 250mg/day for 12-24 weeks achieved a 46% complete cure rate at 48 weeks[6] in Phase III studies. Notwithstanding higher efficacy and shorter treatment courses, adverse events have held oral agents back from commercial success[7]. Alternatives in this category include oral fluconazole (prescribed off-label to patients who cannot tolerate itraconazole or terbinafine)[8] or griseofulvin (500-1000mg per day for 12-18 months).
    b) Topical generics are also considered as the first prescription-only option, particularly where systemic agents are contraindicated or not tolerated. Until recently, the only generic topical available was ciclopirox (PENLAC[9]) which in 2010 accounted for 1.6M total filled prescriptions. In December 2020 generic versions of KERYDIN became available.

Figure 5. Tetra's tolnaftate formulations are one example of OTC products made available via physicians and pharmacies in the non-prescription segment of the market.

Source: Tetra Corporation

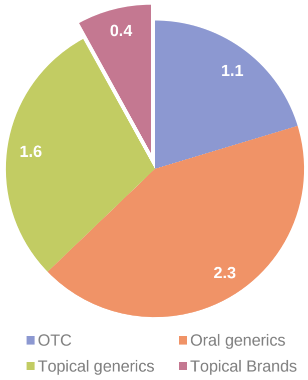
[1] Ameen, M. *et al.* (2014) *British Association of Dermatologists' guidelines for the management of onychomycosis 2014* BJD 171: 937 – 958.
[2] Halteh, P. *et al.* (2016) *OTC and natural remedies for onychomycosis: do they really work?* Cutis 98: E16-E25.
[3] SPORONOX is an oral form of the anti-fungal agent itraconazole approved by FDA in 1992. Generic itraconazole is widely prescribed for a range of fungal infections including onychomycosis.
[4] LAMISIL is a tableted form of the anti-fungal agent terbinafine. FDA approved LAMISIL in 1996 (Novartis as sponsor). The product was broadly genericised from 2007.
[5] Gupta, A. K. *et al.* (1998) *Itraconazole for the treatment of onychomycosis* Int. J. Dermatol. 37: 303 – 308.
[6] Drake, L. A. *et al.* (1997) *Oral terbinafine in the treatment of toenail onychomycosis: North American multicentre trial* J. Am. Acad. Dermatol. 37: 740 – 745.
[7] Hu, Y. *et al.* (2005) Study on the compliance and safety of the oral antifungal agents for the treatment of onychomycosis. Zhonghua Liu Xing Bing Xue Za Zhi. 26(12):988–991.
[8] Al-Hatmi, A. M. *et al.*(2015) Proximal subungual onychomycosis caused by Fusarium falciforme successfully cured with posaconazole. Br J Dermatol. 173(1): 253–5.
[9] PENLAC was the first approved topical treatment for onychomycosis. FDA approved PENLAC in 1999. Seven generics were approved in September 2007.

- **Prescription-only, topical medications**. The 2014 approvals of JUBLIA[10] (efinaconazole) and KERYDIN (tavaborole) changed the market by positioning onychomycosis as a medical, rather than cosmetic, condition. JUBLIA was a material advance in topical efficacy with complete cure rates (15.2% to 17.8%) superior to that of generic ciclopirox (5.5% to 8.5%). Prescription-only topicals remain high price therapies, noting that the published average wholesale price (AWP) for JUBLIA is US$722 for a 4 mL bottle and a complete course of therapy requires up to 10 bottles over a year. Accordingly, payers seek to limit access.

3.1.2 Market structure

Prior to the 'medicalisation' of onychomycosis in 2014 the prescription segment of the market preferred oral systemic drugs on the basis of efficacy (~70% share when we include off-label fluconazole). The availability of JUBLIA lifted the topical category to near parity with oral drugs and that remains the case today (**Figure 6**). The static nature of the prescription market (**Figure 7**) is at odds with epidemiological research which suggests onychomycosis prevalence is increasing as major market patient populations age. We rationalise this with three observations: a) a failure of medical education with low knowledge levels in primary care both blocking referrals to podiatry/dermatology and resulting in the use of ineffective OTC options; b) dissatisfaction with approved molecules with strong anecdotal feedback that real world efficacy is materially lower than that reported in Phase III trials; and finally, c) no innovation in the category by drug developers.

Figure 6. Estimated US onychomycosis market structure in 2020 (filled prescription/dispensing basis). Units: millions.



Source: Wilsons' estimates

Figure 7. Estimated US written prescriptions for branded and generic onychomycosis agents 2010-2021.

Source: Company reports, Bloomberg, Wilsons' estimates

[10] JUBLIA is the North American brand for 10% eficonazole solution, indicated for the treatment of onychomycosis. The product was originally developed by Kaken Pharmaceutical (Japan) and launched in North America by Valeant (now part of Bausch Health Care).

3.1.3 Market outlook

Limited organic growth or structural change until at least 2026. To the best of our research efforts we can find no other topical or oral agent in late stage development capable of changing the market. We have considered the potential approval of Moberg Pharma's MOB-015 (topical terbinafine) because it has completed two Phase III studies. Our view is that MOB-015 is likely to fail commercially (if approved and launched) on the basis of its low complete cure rate (4.5%). We provide more analysis of the onychomycosis development pipeline in **Appendix A2, Table 14.** Two potential catalysts for change in 2026 are: a) the availability of generic JUBLIA (gJublia); and b) the approval and launch of Hexima's pezadeftide.

The availability of gJublia deserves consideration as this event would reset the pricing-versus-efficacy equation for the category. FDA has approved four abbreviated new drug applications (ANDAs) for gJublia[11] but none have launched. Bausch Health Care (BHC) has patent term surviving until February 2026 [12]. BHC's US Patent 7,214,506 was invalidated in 2018 but that decision was overturned in 2020 and as result, it remains enforceable. BHC reached settlement with Acrux and other approved ANDA holders but the terms of that agreement are confidential. Our market model assumes that gJublias are delayed until the expiry of BHC's '506 patent with the caveat that BHC does reference 14 additional patents in FDA Orange Book with potential expiries ranging 2028-2035. Note also that BHC has FDA Data Exclusivity to 2023 and another 6 months of potential protection under paediatric exclusivity.

Prescription topical market can grow if market acess, efficacy and adherance are improved. Long treatment courses, low success rates and high drug pricing impedes the growth of the topical prescription market. JUBLIA is the leading prescripition-only topical with a published average wholesale price (AWP) of US$772 for a 4 mL bottle and US$1,544 for 8 mL[13]. High price has been a deterrent to prescribing with most prescription drug insurance plans limiting access by putting JUBLIA on lower formulary tiers, imposing co-pays on patients (up to US$65 for the initial precription and US$25 for refills) and enforcing step-edits. In practice, patients are required to try generic ciclopirox before qualifying for partial JUBLIA reimbursement. Analysis of Bausch Health's (BHC) US JUBLIA sales data reveals net pricing of ~US$150 per prescription implying gross-to-net deductions of up to 70%. The gap between the published AWP and BHC's implied net pricing includes: a) wholesale distribution margins; b) patient assistance plans (co-pay cards, coupons); c) rebates witheld by PBMs; d) returns or stock obsolescence adjustments. We assess that JUBLIA prescriptions are still growing modestly but BHC's net pricing is declining, suggesting higher rebates to maintain the product on formularies.

Table 5. US market JUBLIA prescriptions, net sales and pricing data

	FY18	**FY19**	**FY20**	*1Q21*	*2Q21*
US net sales (US$M)	**55**	**67**	**69**	14.0	15.0
- sales growth v pcp		*21.8%*	*3.0%*	*-26.3%*	*-6.3%*
TRx	**410,399**	**346,929**	**375,014**	93,528	103,433
- TRx growth		*-15.5%*	*8.1%*	*9.0%*	*17.9%*
US$/Rx	**134**	**193**	**184**	150	145
-Price changes		*44.1%*	*-4.7%*	*-32.4%*	*-20.5%*

Source: Bausch, Bloomberg, Wilsons

The availability of gJublia does not have a large impact on our outlook for the market or pezadeftide's position within it. Our assessment is that both gJublias and new topical brands can enter this market at a discount to JUBLIA and enjoy greater commercial success with more acceptance by payers and PBMs.

[11] FDA has approved abbreviated new drug applications for Aurobindo, Padagis, Teva and Acrux. Acrux submitted an ANDA with a Paragraph IV patent certification in 2018. Acrux announced settlement of the Paragraph IV patent litigation on 3 April 2019 with Valeant (now a subsidiary of Bausch Health). Acrux is pursuing licensing negotiations to commercialise generic efinaconazole.
[12] FDA Orange Book lists 15 patents protecting JUBLIA. The last of these will expire in February 2026 unless invalidated. We note Data Exclusivity extends to April 2023.
[13] IQVIA data

Thoughts on onychomycosis market expansion. Pezadeftide may serve to increase patient participation noting that today's topical prescription market (branded and generic) only services 10% of the total US onychomycosis population. Prevalence estimates for onychomycosis vary between 1% and 8% of the total population[14] (~ 23M patients versus the 2M total prescriptions for JUBLIA, KERYDIN and generic ciclopirox). Factors to consider in the market outlook include:

- **Greater participation taking share from OTC**. The availability of a short-course topical with superior efficacy should encourage more untreated patients to seek therapy. We expect the prescription market to grow at the expense of OTC.
- **Compliance with filling prescriptions**. We estimate a 30%-50% discrepancy between written prescriptions and total filled prescriptions for JUBLIA. Evidence suggests only 1.2 to 1.5 prescription fills per patient implying high rate of discontinuation (standard treatment course being 10-12 bottles). Greater adherence to treatment should grow the market.
- **Pezadeftide can win in both 1st and 2nd line topical prescription segments if priced pragmatically**. Pricing strategy will ultimately depend on efficacy level but our initial view is that pezadeftide should price at a material discount to JUBLIA and at a modest premium to generics. Theoretically pezadeftide should take share from ciclopirox in the 1st line market on efficacy and beat JUBLIA in the 2nd line market on price (and potentially efficacy).
- **Under-served patient groups**. The populations most in need of treatment are the elderly, those with severe disease, the immunocompromised and patients with lower extremity circulation insufficiency including diabetics.
- **Paediatrics**. Prevalence among children is very low (<1%) but topical treatments are strongly favoured. Paediatric development can also add a 6-month extension to patent term.
- **Prophylaxis**. Relapse or reinfection rates after successful treatment can be >50%[15] opening the potential for a secondary prevention market extension.

[14] Bodman, M. A. and Krishnamurthy, K. (2021) *Onychomycosis*. StatPearls.
[15] Gupta, A. K. et *al.* (2020) *Onychomycosis: a review* JEADV 34: 1972 – 1990.

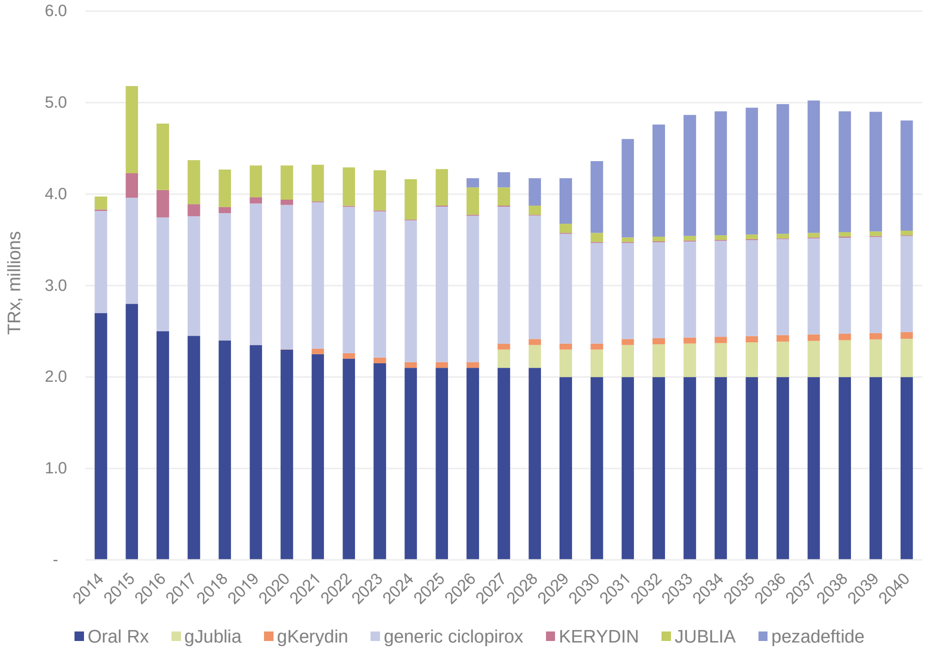
3.2 Pezadeftide outlook

3.2.1 US Forecasting basis

Estimated pezadeftide peak sales of US$250M in US market. At its height in 2015 JUBLIA achieved net sales US$338M from approximately 1M prescriptions. The starting point for our analysis is actual total prescription (TRx) data for topical incumbents JUBLIA, KERYDIN, generic ciclopirox and generic tavaborole. We assess 2.1M total topical prescriptions in that market for 2021 of which >75% is generic ciclopirox. At peak, we estimate 1.5M annual filled prescriptions for pezadeftide which would represent 50% market share in the topical category and 30% market share more broadly (including orals). Our thinking on target product specification to achieve this level of uptake:

- **Short course of treatment**. All approved topical competitors are labelled for a 48-week treatment course. Our base case assumption is a 12-36 week schedule (3 bottles per course) which would be a decisive competitive advantage.
- **Focus on treatment compliance/adherence**. The pairing between the pharmaceutical product and a smartphone app to record and monitor treatment progress would be well received by physicians, payers and patients. If pezadeftide treatment can elicit visible improvements quickly, patients will be more likely to continue and complete the course of therapy, maximising their prospects of a complete cure.
- **Clinical cure rate 15%-20%**. Hexima's Phase IIB is a 9-month study and data may reveal a modest improvement on the mycological cure achieved after 6 weeks treatment in Phase IIA but anything above 50% would be acceptable. The correlation between mycological and complete cure (drawn from prior Phase III studies) suggests a clinical cure rate 15%-20% could be achievable with pezadeftide (noting 14% of patients achieved 90% clear nails after 6-weeks, which should improve with time as the toenail continues to grow out with the infectious fungi killed).
- **Competitive dynamics post JUBLIA generics**. JUBLIA remains the leading branded topical medication with 2020 net sales of US$110M. gJublia presents a great opportunity for the right generic manufacturer because JUBLIA is egregiously overpriced and there is probably a 0.6M prescription market that can be taken away from ciclopirox. Our view is that gJublias are unlikely to grow the topical prescription market as Bausch Health will probably stop promotional activities.
- **Branded market uncontested**. If BHC withdraws marketing support from JUBLIA post-generics it leaves the ~0.5M prescription market uncontested. Pezadeftide is the only new chemical or biological entity in mid-stage clinical development and looks likely to dominate that 2nd line market.
- **Pricing**. We have assumed that pezadeftide is launched at a lower AWP than branded JUBLIA to encourage formulary access with Pharmacy Benefits Managers and rapid adoption. Pricing power will be a function of comparative efficacy, which remains to be confirmed. Market access strategies need to optimise net sales per script whilst providing adequate incentives to other stakeholders (PBMs, health insurers, patients and wholesalers).

Figure 8. Summary US onychomycosis market model has pezadeftide reaching 30% prescription share and net sales ~US$250M.



Source: Company reports, Bloomberg, Wilsons' estimates.

3.2.2 Model projections

Model structure accesses patients from OTC, 1st-line generic and 2nd-line branded. We elected to model pezadeftide in all markets where topical solutions are considered. Summary results are described in **Table 6** below. For each category we have made two fundamental assumptions: a) target peak share; and b) an average percentage of patients with adequate insurance coverage. Furthermore, we assume compliance is 67% or in dosing terms, on average, patients obtain only 2 of the 3 bottles indicated. We have assumed pricing of US$300 per bottle on an AWP basis and assume 40% gross to net deduction in preparing our net sales projections.

Table 6. Pezadeftide model structure and peak net sales estimates

Market segment	OTC	1st Line	2nd Line	Total
Annual prescriptions (M)	1.1	1.6	0.5	**3.2**
TAM (US$M)	$990M	$1,440M	$450M	**$2,880M**
Target peak category share	10%	40%	65%	**36%**
Average payer coverage	60%	55%	65%	**58%**
Treatment compliance	65%	65%	65%	**65%**
Peak net sales estimate (US$M)	$35M	$127M	$88M	**$250M**

Source: Wilsons' estimates

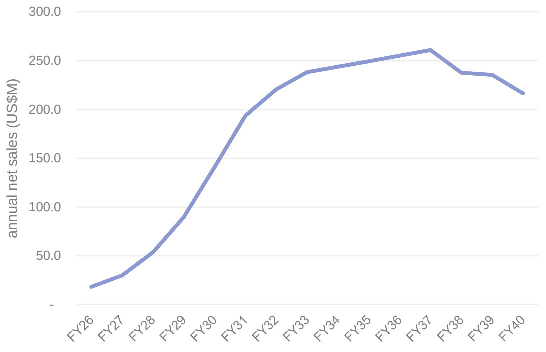
Approval and launch assumptions. We have provided a snapshot of the model over the page in **Table 7** showing a launch year of 2026. Given that each of the three model components are capped by a peak share estimate, our time series forecasts are based on reaching 90% of peak in the sixth year from launch. The resulting time series net sales profile is provided in **Figure 9**.

Table 7. Market model describing US pezadeftide net sales estimates FY23-38e

	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30	FY31	FY32	FY33	FY34	FY35	FY36	FY37	FY38
North America - pezadeftide model																
USA																
Retail OTC population ('000s)	1,000	1,013	1,025	1,038	1,051	1,064	1,077	1,091	1,104	1,118	1,132	1,146	1,161	1,175	1,190	1,205
% peak share switching	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
% with payer coverage	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*
ex-OTC pezadeftide Rx population ('000s)	62	63	64	65	66	66	67	68	69	70	71	72	73	73	74	75
1st Line topical Rx population ('000s)	1,500	1,519	1,538	1,557	1,576	1,596	1,616	1,636	1,657	1,677	1,698	1,720	1,741	1,763	1,785	1,807
% peak share switching	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*
% with payer coverage	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*
1st Line pezadeftide population ('000s)	330	334	338	343	347	351	356	360	364	369	374	378	383	388	393	398
2nd Line topical Rx population ('000s)	500	506	513	519	525	532	539	545	552	559	566	573	580	588	595	602
% peak share switching	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*
% with payer coverage	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*	*65%*
2nd Line pezadeftide population ('000s)	217	219	222	225	228	231	233	236	239	242	245	248	251	255	258	261
Total pezadeftide population ('000s)	609	617	624	632	640	648	656	664	673	681	690	698	707	716	725	734
% treatment compliance	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*	*67%*
# pezadeftide units ('000s)	1,218	1,234	1,249	1,265	1,280	1,296	1,313	1,329	1,346	1,362	1,379	1,397	1,414	1,432	1,450	1,468
Gross ASP (US$/pezadeftide unit)				300	300	300	300	300	300	300	300	300	300	300	300	300
% progress to peak share	*0%*	*0%*	*0%*	*8%*	*13%*	*23%*	*38%*	*59%*	*80%*	*90%*	*96%*	*97%*	*98%*	*99%*	*100%*	*90%*
Gross sales (US$M)	-	-	-	30.3	49.9	89.4	149.6	235.2	322.9	367.8	397.3	406.4	415.8	425.2	434.9	396.3
% gross to net deduction				*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*
pezadeftide net sales (US$M)	**-**	**-**	**-**	**18.2**	**30.0**	**53.7**	**89.8**	**141.1**	**193.8**	**220.7**	**238.4**	**243.9**	**249.5**	**255.1**	**260.9**	**237.8**

Source: Wilsons' estimates

Figure 9. US pezadeftide net sales estimates FY26-40e



Source: Wilsons' estimates

Our assessment attempts to capture a conservative base case outlook for pezadeftide. Other considerations:

- **Market growth**. Model assumes 1.25% annual growth in the treatment population. The availability of pezadeftide drives topical category share to 60% (estimate 48% share in 2021).
- **Static pricing**. We have not included any price increases in our forecasts.
- **Exclusivity**. We have assumed formal patent term to 2035-6, extendable by 6 months with paediatric exclusivity. Note that pezadeftide may be eligible for 12 years protection from the date of FDA approval as a novel biologic. This latter form of protection is: a) independent of patent rights; b) precludes competitors filing a biosimilar application for 4 years after approval; and c) prevents FDA approving a biosimilar for a further 8 years after approval. Expiry: 2038 in USA.

3.3.2 Japanese forecasting basis

Exclusive partnering model adopted for Japanese pezadeftide rights. We have chosen a revenue model for Japan based on milestone payments and royalties received by Hexima under exclusive licence. Transaction assumptions include:

- Transaction settled in 2024 after positive Phase III trial results with upfront payment of US$25M.
- US$15M milestone payment triggered by PDMA approval.
- Low double-digit percentage royalties on net sales.
- Additional milestone payments of up to US$125M based on cumulative net sales targets.
- In NPV terms, Hexima's royalties and milestone payments are weighted 45:55.
- We have assumed the Japanese partner achieves 95% gross margin and incurs incremental SG&A expense of 25% of net sales.
- In NPV terms, Hexima's share of overall project NPV is 42%.

Table 8. Key jurisdictional assumptions

Pezadeftide	USA	Japan
Launch year	2026	2026
Exclusivity period	2038	2035
Peak net sales (US$M)	250	115
Addressable population (M)	3.2	2.5
Maximum patient penetration	36	20%
TAM (US$B)	2.9	2.4

Source: Wilsons' estimates

Table 9. Summary model for exclusive partnering of pezadeftide's Japanese rights

	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30	FY31	FY32	FY33	FY34	FY35	FY36
Japan - pezadeftide partnering model														
Japan														
Japanese partner pezadeftide net sales (US$M)	**-**	**-**	**-**	**17.4**	**36.3**	**53.5**	**67.2**	**78.5**	**85.2**	**92.3**	**95.9**	**97.1**	**98.4**	**100.0**
cumulative net sales (US$M)				17	54	107	174	253	338	430	526	623	722	822
COGS	-	-	-	0.9	1.8	2.7	3.4	3.9	4.3	4.6	4.8	4.9	4.9	5.0
Royalties to Hexima	**-**	**-**	**-**	**2.1**	**4.4**	**6.4**	**8.1**	**9.4**	**10.2**	**11.1**	**11.5**	**11.7**	**11.8**	**12.0**
Gross profit (US$M)	-	-	-	14.5	30.1	44.4	55.8	65.1	70.7	76.6	79.6	80.6	81.6	83.0
- gross margin				*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*	*83.0%*
Commercial payments to Hexima	**-**	**25.0**	**-**	**15.0**	**-**	**15.0**	**-**	**15.0**	**-**	**-**	**30.0**	**-**	**-**	**-**
Incremental SG&A (US$M)	-	5.0	10.0	10.0	9.1	13.4	16.8	19.6	21.3	23.1	24.0	24.3	24.6	25.0
pezadeftide EBITDA contribution	**-**	**(30.0)**	**(10.0)**	**(10.5)**	**21.1**	**16.1**	**39.0**	**30.5**	**49.4**	**53.5**	**25.7**	**56.3**	**57.1**	**58.0**
- pez EBITDA contribution margin					*58.0%*	*30.0%*	*58.0%*	*38.9%*	*58.0%*	*58.0%*	*26.7%*	*58.0%*	*58.0%*	*58.0%*
Japanese partner pezadeftide cash flow (US$M)	**-**	**(30.0)**	**(10.0)**	**(10.5)**	**21.1**	**16.1**	**39.0**	**30.5**	**49.4**	**53.5**	**25.7**	**56.3**	**57.1**	**58.0**
Hexima pezadeftide cash flow (US$M)	**-**	**25.0**	**-**	**17.1**	**4.4**	**21.4**	**8.1**	**24.4**	**10.2**	**11.1**	**41.5**	**11.7**	**11.8**	**12.0**
Partner project NPV	**159.9**													
Hexima project NPV	**118.1**													

Source: Wilsons' estimates

3.3 Investment and expense assumptions

Cash. Hexima had $3.4M cash as at 30 June 2021. Hexima recently raised an additional $10M via institutional placement to finance preparatory projects enabling a Phase III campaign in 2022 assuming supporting Phase IIB results. FY23 and FY24 are anticipated to be high cash burn years given the significant R&D expenses that will be incurred for the Phase III clinical trials.

Expense assumptions include the following:

COGS and gross profit margin. Pezadeftide is manufactured by a CDMO using an off-patent cell culture expression system with *Picchia pastoris* as the process organism. At the pricing assumptions in our model we expect gross margins of 95% or greater.

R&D expense. The majority of our R&D expense forecast relates to the Phase III trial campaign planned for pezadeftide. The forecast also accommodates ancillary clinical and non-clinical research to further elucidate mechanism of action and explore pezadeftide's utility in other indications.

SG&A expense. Hexima has modest operating expenses outside its R&D activities. We have made SG&A estimates that position pezadeftide as a 55% EBITDA contribution asset.

Tax. Hexima reported accumulated net losses of $71M at the end of FY20. We do not anticipate material cash tax payments until 2030+. In the meantime, Hexima is eligible to receive R&D tax rebates based on R&D expense plans.

Capex. Hexima is an infrastructure light business with minimal capex requirements. We do not forecast any substantive capex investments for Hexima in our forecast period.

3.4 Forecasts and funding requirements

Table 10. Long term financial statement projections FY22-32e

	FY22	FY23	FY24	FY25	FY26	FY27	FY28	FY29	FY30	FY31	FY32
Income statement											
Commercial revenue	-	-	33.3	-	22.8	5.8	28.6	10.8	32.6	13.6	14.8
Product sales	-	-	-	-	24.3	39.9	71.6	119.7	188.2	210.3	257.6
Total revenue	**-**	**-**	**33.3**	**-**	**47.1**	**45.8**	**100.1**	**130.5**	**220.7**	**223.9**	**272.4**
COGS	-	-	-	-	(1.2)	(2.0)	(3.6)	(6.0)	(9.4)	(10.5)	(12.9)
Gross Profit	0.0	0.0	33.3	0.0	45.9	43.8	96.5	124.5	211.3	213.4	259.5
margin %	***0%***	*0%*	*0%*	*0%*	*97%*	*96%*	*96%*	*95%*	*96%*	*95%*	*95%*
Operating Expenses											
General operating expense	(4.5)	(4.9)	(5.3)	(5.8)	(6.4)	(7.0)	(7.7)	(8.5)	(9.2)	(10.1)	(9.5)
US pezadeftide SG&A	-	-	-	(16.7)	(34.3)	(36.7)	(40.0)	(83.2)	(89.9)	(97.0)	(104.8)
R&D	(4.5)	(10.0)	(18.0)	(27.0)	(29.4)	(32.4)	(35.6)	(39.2)	(27.9)	(30.7)	(9.5)
D&A	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)	(0.3)	(6.9)	(8.0)	(9.6)
	-	-	-	-	-	-	-	-	-	-	-
EBIT	(9.3)	(15.2)	9.7	(49.8)	(24.6)	(32.6)	13.0	(6.7)	77.5	67.5	126.1
EBITDA	**(9.0)**	**(14.9)**	**10.0**	**(49.5)**	**(24.3)**	**(32.3)**	**13.3**	**(6.4)**	**84.4**	**75.5**	**135.7**
EBITDA margin			*30%*				*13%*		*38%*	*34%*	*50%*
Net interest expense/finance costs	-	-	-	-	-	-	-	-	-	-	-
Profit (Loss) before tax (EBT)	(9.3)	(15.2)	9.7	(49.8)	(24.6)	(32.6)	13.0	(6.7)	77.5	67.5	126.1
Tax (expense)/credit	-	-	-	-	-	9.8	(3.9)	2.0	(23.2)	(20.3)	(37.8)
NPAT	**(9.3)**	**(15.2)**	**9.7**	**(49.8)**	**(24.6)**	**(22.8)**	**9.1**	**(4.7)**	**54.2**	**47.3**	**88.3**
	-	-	-	-	-	-	-	-	-	-	-
Balance sheet	-	-	-	-	-	-	-	-	-	-	-
Total current assets	46.0	36.1	144.2	95.8	75.6	53.2	61.7	58.4	99.6	147.0	230.7
Total Non-current assets	1.4	1.7	2.0	2.3	2.6	2.9	3.2	3.5	3.8	4.1	4.4
Total Assets	**47.4**	**37.8**	**146.2**	**98.1**	**78.3**	**56.1**	**64.9**	**61.9**	**103.4**	**151.1**	**235.1**
Total current liabilities	1.1	7.0	16.7	17.5	22.5	23.5	23.5	25.5	13.1	13.8	9.9
Total non-current liabilities	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Total liabilities	**2.7**	**8.6**	**18.3**	**19.1**	**24.1**	**25.1**	**25.1**	**27.1**	**14.7**	**15.4**	**11.5**
Equity											
Contributed equity	122.4	122.4	222.4	222.4	222.4	222.4	222.4	222.4	222.4	222.4	222.4
Reserves	2.8	2.5	(8.5)	(7.6)	(7.9)	(8.2)	(8.6)	(8.9)	(9.2)	(9.5)	(9.8)
Accumulated Profit/losses	(80.4)	(95.6)	(86.0)	(135.8)	(160.3)	(183.1)	(174.0)	(178.7)	(124.5)	(77.2)	11.1
Total equity	**44.7**	**29.2**	**127.9**	**79.0**	**54.1**	**31.0**	**39.8**	**34.8**	**88.7**	**135.7**	**223.6**
	-	-	-	-	-	-	-	-	-	-	-
Cashflow statement	-	-	-	-	-	-	-	-	-	-	-
Total cash flow from operations	(9.8)	(10.0)	11.6	(48.7)	(14.9)	(21.7)	6.0	(4.4)	36.7	48.5	81.7
Total cash flows from investing activities	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)	(0.6)
Cash flows from financing activities											
Debt issued											
Proceeds from issue of shares (net)	50.5	-	100.0	-	-	-	-	-	-	-	-
Net cash flow from financing activity	48.4	(0.0)	96.0	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Cash at End of the half year	**41.5**	**30.8**	**137.8**	**88.5**	**73.0**	**50.6**	**56.1**	**51.1**	**87.2**	**135.0**	**216.1**

Source: Wilsons

Appendices

A1. Onychomycosis

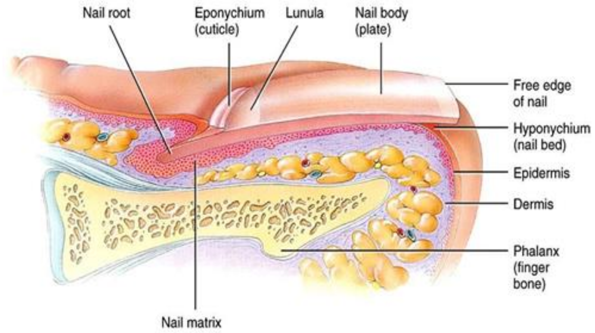
A1.1 Clinical presentation

Onychomycosis is fungal infection of the nail caused by dermatophytes, non-dermatophyte moulds, and yeasts[16]. All nails are susceptible but toenail involvement is most common. The condition presents as nail discolouration, thickening (hyperkeratosis) and separation of the nail from the underlying nailbed (onycholysis). If left untreated onychomycosis can lead to the complete destruction of the nail plate (Figure 10). The chronic impact of the infection includes discomfort, anxiety, stigmatisation and psychological distress due to its appearance[17]. Untreated onychomycosis in elderly, diabetic or immunocompromised patients can lead to secondary foot infections and ulceration[18]. Onychomycosis is a challenging condition to treat because it is easily acquired through contact with invading fungal species[19], which become sequestered beneath the nail plate (Figure 11). Toenails are particularly susceptible, lacking effective cell-mediated immunity, and are prone to repeated cycles of reinfection[20]. Accurate diagnosis relies on the identification of the causative pathogen using culture techniques and microscopy.[21].

Figure 10: Onychomycosis is a fungal infection leading to the destruction of nails.

Source: Leung (2020)[22]

Figure 11: Anatomical features of the toe and toenails



Source: Mayo Clinic

A1.2 Epidemiology

The overall worldwide prevalence of onychomycosis in the general population is approximately 5.5%, based on peer reviewed epidemiological studies[23]. Prevalence is slightly lower in the major European and North American markets but still over 4.3% (95% confidence interval: 1.9% to 6.8%) in a population-based analysis published in 2014[24]. Those statistics would imply a potential treatment population of up to 23M today. There is evidence that the prevalence is rising, possibly because of longer life expectancy and the unchecked propensity for Western populations to develop obesity and peripheral circulation problems. The condition is more common in adults than in children and the prevalence increases with age, and is as high as 35% in the elderly[25]. Toenail onychomycosis is more common in males whereas *Candida* fingernail onychomycosis is more common in females.

---

[16] Gupta, A. K. et al. (2014) *Molecular determination of mixed infections of dermatophytes and non-dermatophyte moulds in individuals with onychomycosis* J. Am. Podiatr. Med. Assoc. 104: 330 – 336.
[17] Belyayeva E. et al. (2013) *The impact of nail disorders on quality of life*. Eur J Dermatol. 23(3):366-371.
[18] Gupta A. K. et al. (1998) *Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey*. Br J Dermatol. 139(4):665-671.
[19] The most common infecting fungal groups are Trichophyton spp., Microsporum spp. and Epidermophton spp. which are thought to cause 90% of cases. Non-dermatophyte moulds (Scopulariopsis spp., Aspergillus spp.) may co-infect with dermatophytes leading to incorrect diagnosis, treatment failure and relapse. The yeast species Candida spp. is associated with approximately 5% of cases.
[20] Lipner, S. R. and Scher, R.K. (2019) Onychomycosis: Clinical overview and diagnosis. J Am Acad Dermatol 80(4): 835-51.
[21] Ghannoum, M. et al. (2014) *Fungal nail infections(onychomycosis): a never-ending story?* PLoS Pathog. 10(6): e1004105.
[22] Leung, A. K. C. et al. (2020) *Onychomycosis: an updated review* Recent Patents on Inflammation & Allergy Drug Discovery 14, 32-45
[23] Jacobson, T. J. et al. (2010) *Toenail onychomycosis: An important global disease burden*. J Clin Pharm Ther. 35(5): 497-519.
[24] Sigurgeirsson, B. and Baran, R. (2014) *The prevalence of onychomycosis in the global population: A literature study*. J Eur Acad Dermatol Venereol 28(11): 1480-91.
[25] Cozzani, E. et al. (2016) Epidemiological study of onychomycosis in older adults with onychodystrophy. Geriatr Gerontol Int 16(4): 486-91.

Table 11. Onychomycosis subtypes

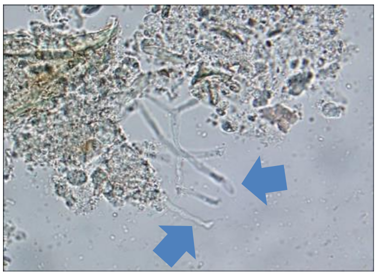
Subtype	Clinical description	Example
Distal lateral subungual onychomycosis	In distal lateral subungual onychomycosis, the fungal invasion begins at the hyponychium and then progresses to involve the distal nail bed and subsequently the nail plate. The fungus then migrates proximally through the nail plate, causing linear channels or "spikes". This clinical subtype is usually caused by *Trichophyton rubrum* and less commonly by *Trichophyton mentagrophytes.* Clinically, distal lateral subungual onychomycosis presents as yellowish, whitish, or brownish discoloration of a distal corner of a nail. Distal subungual hyperkeratosis, onycholysis, and/or onychauxis of the lateral and distal aspects of the nail plate are common[26].	
White superficial onychomycosis	In white superficial onychomycosis, the upper surface of the nail plate is affected by the fungus, notably *Trichophyton mentagrophytes.* Typically, white superficial onychomycosis presents as white dots or patches on the surface of the nail plate. The white dots and patches can be easily scraped off.	
Proximal lateral subungual onychomycosis	Proximal subungual onychomycosis develops when the fungus invades the under-surface of the proximal nail fold in the vicinity of the cuticle and then extends distally. This clinical subtype is usually caused by *Trichophyton rubrum* and *Fusarium spp.*[27] Clinically, proximal subungual onychomycosis presents as an area of leukonychia in the proximal nail plate and moves distally with nail growth. Proximal subungual onychomycosis usually occurs in patients with immunodeficiency especially Acquired Immunodeficiency Syndrome (AIDS).	
Endonyx onychomycosis	Endonyx onychomycosis is caused by fungal infection of the nail plate without infection of the nail bed. This clinical subtype is usually caused by *Trichophyton soundanense* and *Trichophyton violaceum*. Clinically, endonyx onychomycosis is characterized by milky patches of the nail plate, indentations, and lamellar splitting. The nail plate is firmly attached to the nail bed and subungual hyperkeratosis is absent[28].	
Total dystrophic onychomycosis	Total dystrophic onychomycosis is characterized by the total destruction of the entire nail apparatus and is often the end-stage of onychomycosis that may follow any of the other subtypes. Clinically, total dystrophic onychomycosis presents with a severely dystrophic and crumbed nail plate which is yellowish, diffusely thickened, and friable.	

Source: As referenced, Wilsons

[26] Goldstein, A. O. and Bhatia, N. Onychomycosis: Epidemiology, clinical features, and diagnosis. In: Post TW, ed. Up To Date. Waltham,MA.
[27] Shemer A. (2012). Update: Medical treatment of onychomycosis. Dermatol Ther. 25(6): 582-93.
[28] Piraccini, B. M. and Alessandrini, A. (2015) Onychomycosis: A review. J Fungi (Basel) 1(1): 30-43.

A1.3 Diagnosis

Figure 12. Direct visualisation of *T. rubrum* hyphae in association with nail scapings in KOH wet-mount.



Source: Karaman (2020)[36]

Onychomycosis accounts for 50% of all nail disease and visual inspection is often relied on in primary care (GPs, podiatrists) and dermatology[29]. Differential diagnosis can be challenging because the visual cues bear resemblance to nail changes linked to non-fungal conditions including psoriasis, chronic dermatitis and porphyrias[30]. A definitive diagnosis requires the identification of the infecting species using direct microscopic examination with a potassium hydroxide (KOH) wet-mount preparation or fungal culture of nail samples. In practice, inadequate sampling technique is common, leading to misdiagnosis. In one study, the clinical diagnostic accuracy of onychomycosis among non-dermatologists and dermatologists was approximately 66% and 75%, respectively[31].

A1.4 Standard of care

A1.4.1 Oral medications

Oral antifungal agents used for the treatment of onychomycosis include terbinafine (LAMISIL), itraconazole (SPORANOX) and generic fluconazole prescribed off-label[32]. Of these compounds, terbinafine is favoured given that it is fungicidal (both azole drugs are only fungistatic) and is potentially safer. Terbinafine treatment also has better clinical and mycological cure rates, based on meta-analysis[33]. Oral itraconazole is reserved for those who cannot tolerate or fail terbinafine. Oral itraconazole suffers from wildly different absorption patterns among individuals with headaches, gastrointestinal upset and hepatic dysfunction the most common adverse events. We provide analysis of prescribing habits in Section 3.

A1.4.2 Topical medications

Topical therapy involves applying anti-fungal drug solutions to the top of the nail plate such that the therapeutic agent penetrates through the nail to the site of infection. Nails are a hydrophilic medium and are more permeable to antifungal agents formulated in aqueous vehicles[34]. Commonly used topical antifungal agents include efinaconazole (JUBLIA), tavaborole (KERYDIN), ciclopirox (PENLAC) and less importantly, amorolfine (LOCERYL). We provide detailed analysis of prescribing habits and market structure in Section 3 of this report. Generally, topical antifungal agents are well-tolerated and adverse events are minimal. However, topical therapy requires longer treatment courses (often 48 weeks or longer) and may be less effective than oral treatment possibly because of insufficient nail plate penetration. The impermeability of the nail can be attributed to the highly stable disulfide linkages and hydrogen bonds in the keratin network that forms the nail structure[35].

A1.4.3 Lasers and photodynamic therapy (PDT)

These two modalities are at the fringe of treatment and a side interest from dermatologists' interest in the disease. Neither are adequately scalable to address the disease population. They are also expensive and thus reserved for patients where the oral/topical standard of care is contraindicated or failed. Lasers with wavelengths 750-1,300 nm are required to penetrate the nail with the goal of selectively killing the fungal mycelia by photothermolysis[37]. There is little comparative data available on the effectiveness of lasers but results read no better than available topical or oral therapies[38]. PDT uses specific wavelengths of light to activate photosensitive molecules that have been absorbed by the fungi. Data is scarce and of low quality.

[29] Koshnick, R. L. et *al.* *(2007)* Use of diagnostic tests by dermatologists, podiatrists and family practitioners in the United States: Pilot data from a cross-sectional survey. Mycoses 50(6): 463-9.
[30] Leung, A. K. et *al.* (2019) Melanonychia striata: Clarifying behind the black curtain. A review of clinical evaluation and management of the 21st century. Int J Dermatol 58(11): 1239-45.
[31] Li, D. G. et *al.* (2018) Clinical diagnostic accuracy of onychomycosis: A multispecialty comparison study. Dermatol Res Pract 2018; 2018: 2630176.
[32] DIFLUCAN is indicated for a range of fungal infections including vaginal candidiasis and tineas (superficial infections).
[33] Kreijkamp-Kaspers, S. et *al.* (2017) Oral antifungal medication for toenail onychomycosis. Cochrane Database Syst Rev. 7: CD010031.
[34] Vlahovic, T. C. (2016) *Onychomycosis: Evaluation, treatment options, managing recurrence, and patient outcomes*. Clin Podiatr Med Surg 33(3): 305-18
[35] Dhamoon, R. K. et *al.* (2019) *Novel drug delivery strategies for the treatment of onychomycosis*. Pharm Nanotechnol 7(1): 24-38.
[36] Karaman, B. F. O. et *al.* (2019) *Diagnostic values of KOH examination, histological examination, and culture for onychomycosis: A latent class analysis*. Int J Dermatol 58(3):319-24.
[37] Absorption of laser energy causes escalating cell temperature and death.
[38] Gupta, A. K. and Versteeg, S. G. (2017) *A critical review of improvement rates for laser therapy used to treat toenail onychomycosis*. J Eur Acad Dermatol Venereol 31(7): 1111-1118

A2. Pezadeftide

A2.1 Pezadeftide and its non-clinical characterisation

A2.1.1 Pezadeftide

Pezadeftide is an antimicrobial peptide and an example of a molecular class called plant defensins[39]. Hexima's patent portfolio describes, exemplifies and claims libraries of such molecules which have several conserved features including size, sequence homology and a structure stabilised by disulphide bonding between cysteine (Cys) residues. Hexima's patents also protect protein-engineered, synthetic variants where structures from naturally occurring Class I and Class II defensins have been combined to enhance certain functions including the ability to permeabilise fungal cells or reduced ability to lyse red blood cells.

Pezadeftide is based on a naturally occurring defensin from Florida bitterbush (*Picramnia pentandra*). The drug molecule comprises the native amino acid sequence (Figure 13) with an alanine residue added to its N-terminus. This modification is also specifically claimed in Hexima's patents and is important in enhancing high yield production in recombinant *Pichia pastoris* expression systems.

A2.1.2 Mechanism of action

Pezadeftide is a hydrophilic peptide which is crucial to its performance as a drug and differentiating from other defensins, mechanistically. This compound is thought to associate with fungal cell wall components and be internalised by fungal cells via an endocytosis pathway. Hexima has shown evidence that pezadeftide concentrates on the cell surface before the plasma membrane is disrupted. The first point of difference to note here is the degree of specificity for fungal and not host cells. The canonical interaction between more hydrophobic defensins and their fungal targets is a process of non-specific aggregation within the lipid membrane, forming structures that lyse from the outside-in[40]. As this is a non-specific, physical interaction in most cases, mammalian cells may also be affected[41].

Pezadeftide also has a permeabilising effect on fungal cells but this is likely a consequence of other intracellular damage its internalisation induces. The intracellular component of Pezadeftide's mechanism is yet to be fully elucidated but mitochondrial damage and reactive oxygen species are thought to be central. Anecdotally, intracellular pezadeftide triggers an acceleration in mitochondrial activity, the production of reactive oxygen species and oxidative stress. This internal reaction proves to be lethal in fungal cells through a mix of apoptosis and outer membrane disruption.

A2.1.3 Fungicidal activity

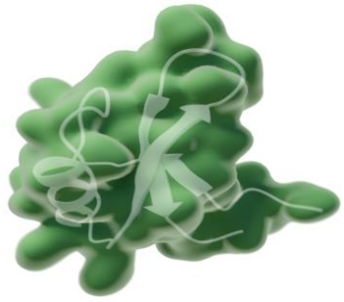
Pezadeftide has antifungal activity against a range of clinically important fungal pathogens including *Candida spp*, *Cryptococcus spp*, dermatophytes and non-dermatophytic moulds. Published results for the three most common *Trichophyton spp.* associated with onychomycosis showed that the drug concentration required to inhibit all visible growth also killed 99.9% of the cells (Figure 16). Higher unit concentrations of pezadeftide are required to kill fungi (compared to efinaconazole) but this ostensible disadvantage is more than offset by higher rates of penetration through the nail plate as shown overleaf in Figure 18.

Figure 13. Pezadeftide amino acid structure.

Ala	Lys	Val	Cys	Thr	Lys	Pro	Ser	Lys	
1									
Phe	Phe	Lys	Gly	Leu	Cys	Gly	Thr	Asp	Gly
10									
Ala	Cys	Thr	Thr	Ala	Cys	Arg	Lys	Glu	Gly
20									
Leu	His	Ser	Gly	Tyr	Cys	Gln	Leu	Lys	Gly
30									
Phe	Leu	Asn	Ser	Val	Cys	Val	Cys	Arg	Lys
40									
His	Cys								
50									

Source: US 10,973,874

Figure 14. Space-filling and ribbon model representations of pezadeftide.



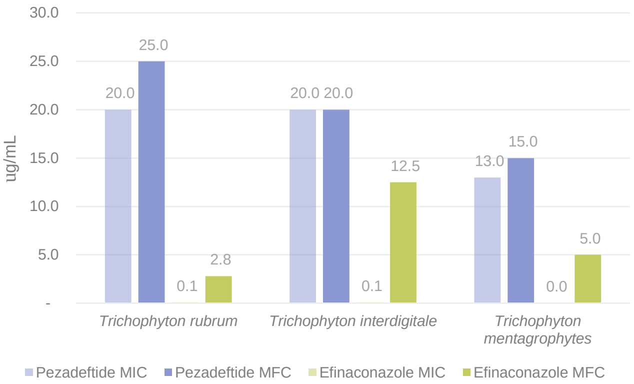
Source: Hexima

Figure 15. Florida bitterbush (*Picramnia pentandra*).

Source: University of Florida Center for Aquatic and Invasive Plants

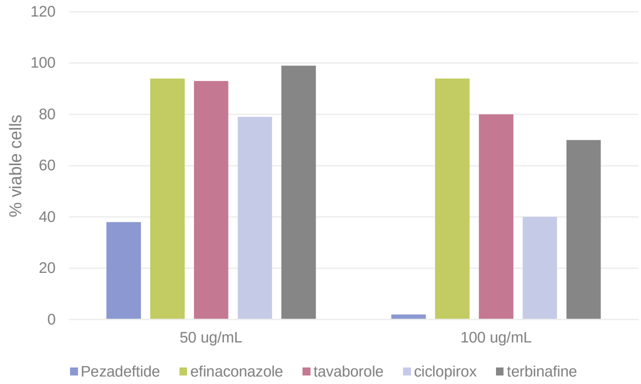
[39] Tam, J. P. et *al.* (2015) *Antimicrobial peptides from plants* Pharmaceuticals 8: 711 – 757.
[40] Sher Khan, R. et *al.* (2019) *Plant defensins: types, mechanisms of action and prospects of genetic engineering for enhanced disease resistance in plants* 3 Biotech 9: 192.
[41] Lichtenstein, A. (1991) *Mechanism of mammalian cell lysis mediated by peptide defensins. Evidence for an initial alteration of the plasma membrane* J. Clin. Invest. 88: 93 – 100.

Figure 16. Minimum inhibitory and fungicidal concentrations are similar for pezadeftide across three *Trichophyton spp.*



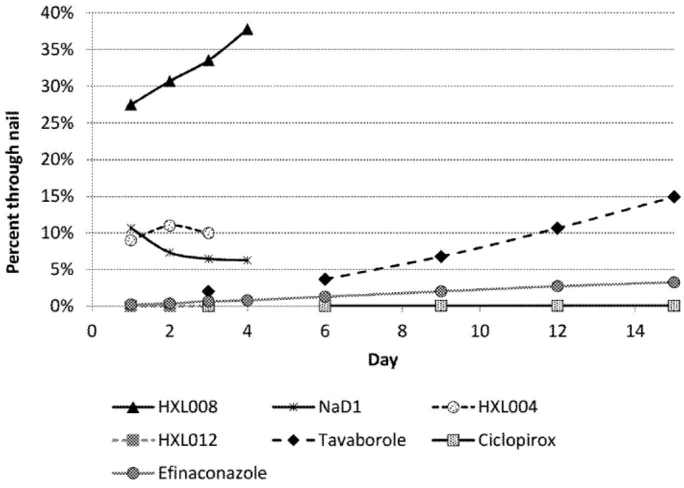
Source: Hexima, Wilsons

Figure 17. Pezadeftide more lethal against *Candida* at 100 µg/mL compared to other anti-fungal agents



Source: Hexima, Wilsons

Figure 18. Pezadeftide (HXL008) has vastly superior penetration through human nails measured according to the method of Hui *et al.* (2002)[42].



Source: US Patent 10,973,874

[42] Hui, X. et al. (2002) *Enhanced human nail drug delivery: nail inner drug content assayed by new unique method* J. Pharm. Sci. 91: 189 – 195.

A2.2 Clinical evidence to support clinical development of pezadeftide

A2.2.1 Phase I/IIA trial (HXP124-ONY-001)

Trial design

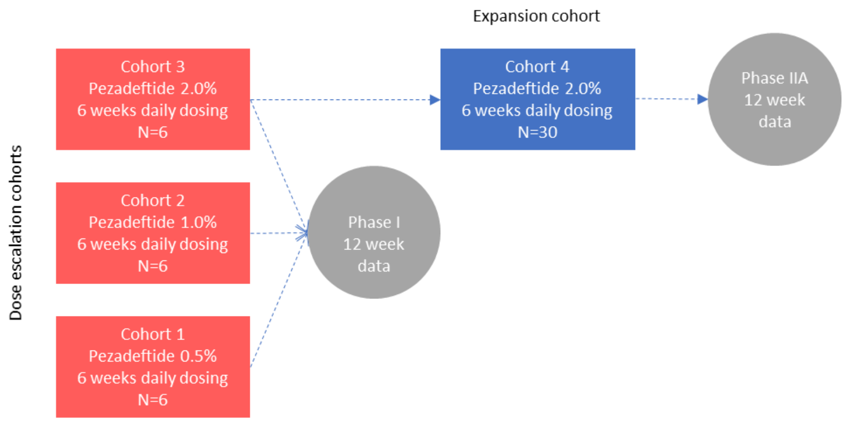
HXP124-ONY-001 was a Phase I/IIA, first-in-human, randomised, double-blind, vehicle-controlled multiple ascending dose study in healthy volunteers with mild-to-moderate onychomycosis (ANZCTR registration number: ACTRN12618000131257)[43]. To be eligible for this study, participants had to be otherwise healthy, aged 18 to 65 years, with onychomycosis confirmed by mycological staining and/or culture. The onychomycosis needed to affect at least 20% but not more than 70% of one (or both) great toenail(s) as determined by visual inspection after the nail had been trimmed.

Primary endpoint: to assess the safety and tolerability of multiple ascending pezadeftide (HXP124) topical doses in participants affected with mild-to-moderate onychomycosis over a dosing period of 6 weeks and follow-up occurring to 12 weeks.

Secondary endpoints: a) assess the markers of effectiveness of pezadeftide in participants with mild-to-moderate onychomycosis receiving multiple ascending pezadeftide topical doses with follow-up of 12 weeks; b) assess the pharmacokinetic (PK) parameters after single and repeated topical doses.

This trial was separated into two components (**Figure 19**). In both Parts 1 and 2, participants administered daily applications of pezadeftide to all 10 toenails, including at least one affected great toenail, for 6 weeks. All patients were followed up at 2 weeks, 6 weeks, 9 weeks and 12 weeks. Part 1 of the study was the dose-ascending phase to assess increasing doses (from 0.5% to 2%) of pezadeftide. Following no safety concerns in Part 1, the top dose of 2.0% was developed with an expansion cohort (Part 2) of 30 patients (randomized 4:1 for active:vehicle).

Figure 19. Phase I/IIA trial design. All cohorts randomised 2:1 (drug:vehicle). Subjects treated daily for 6 weeks with follow-up at 12 weeks.



Source: Hexima, Wilsons.

[43] https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374039

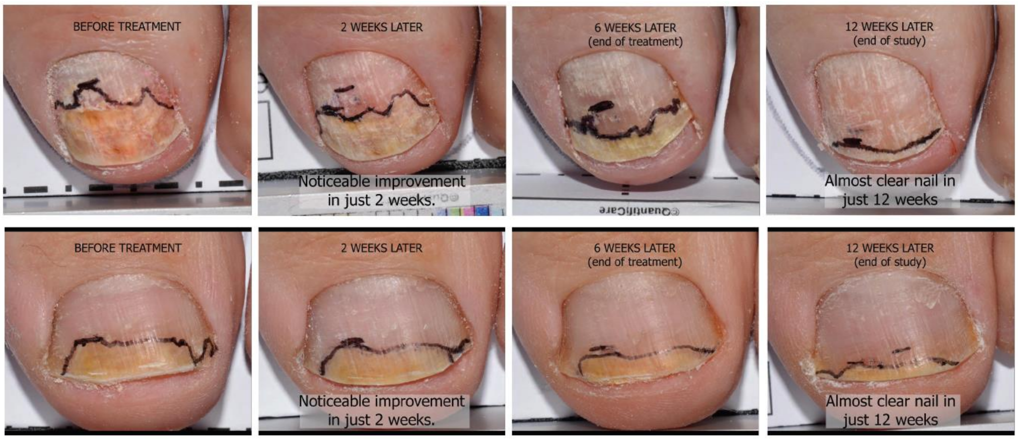
A2.2.1.2 Safety

Pezadeftide appeared to be safe and well-tolerated at all three dose levels (0.5 %, 1.0 %, and 2.0 %) based on observations from all 36 subjects treated. There were no serious adverse events.

- No treatment emergent adverse event (TEAE) led to withdrawal of study drug or premature withdrawal of any participant from the study.
- The majority of TEAEs were mild (< Grade 3) and there were no severe TEAEs reported.
- The incidence of TEAEs was higher for the pooled vehicle group (75%) compared to the pooled pezadeftide-treated group (63.9%). Incidence did not increase with increasing dose.
- No clinically significant changes in vital signs, ECGs, or clinical laboratory parameters were seen.

A2.2.1.3 Efficacy

Figure 20. Photographs of pezadeftide-treated nails over the duration of the Phase I/IIA study



Source: HXL

Mycological cure

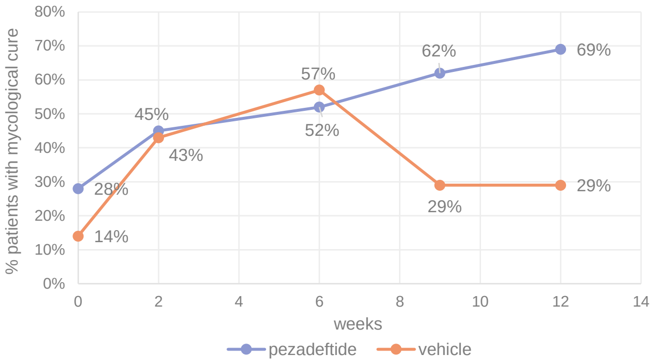
Data. The presence of fungi in the nail was assessed by microscopy and culture of nail clippings and scrapings. Mycological Cure was defined as negative for the presence of fungi by both stain and culture. Patients underwent a mycology screen two weeks before and on the day of study entry (baseline). The Mycological Cure rate (stain and culture negative) at 12 weeks was 69% for pezadeftide-treated nails compared to 29% for vehicle (**Figures 21 & 22**). The Mycological Cure rate in pezadeftide-treated nails increased steadily over time from 27.6% at Baseline to 44.8%, 51.7%, 62.1% and 69.0% at weeks 2, 6, 9, and 12, respectively. Importantly, the rate continued to increase after dosing was stopped. In contrast, vehicle-treated nails demonstrated an initial increase in mycological cure but this reverted to baseline once dosing was stopped (**Figure 21**). If the mycological cures at baseline are omitted from the analysis then the mycological cure rates are 55% for pezadeftide and 17% for vehicle. Results summarised in **Table 12**.

Table 12: Phase IIA cohort 4 analysis of mycological cure

Cohort 4 summary	**Pezadeftide**	**Vehicle**
Patients	24	6
Infected nails	28	7
Mycological cure		
Mycological cures at Wk-0 (n)	8	1
Mycological cure rate at Wk-0 (%)	*29%*	*14%*
Mycological cures at Wk-12 (n)	19	2
Mycological cure rate at Wk-12 (%)	*67.9%*	*28.6%*
Adjusted patient numbers	20	6
Adjusted mycological cures at Wks 2-12 (n)	11	1
Adjusted mycological cure rate at Wks 2-12 (%)	*55%*	*17%*

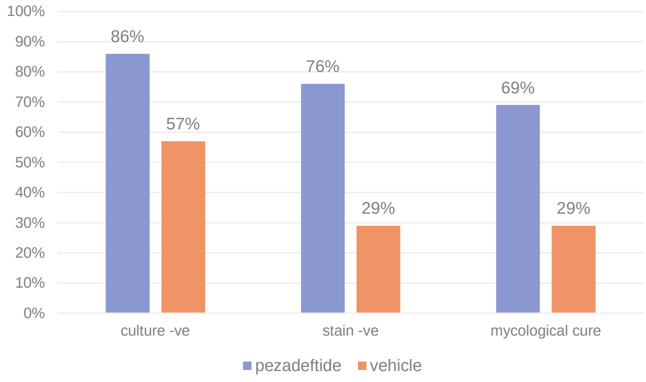
Source: Wilsons

Figure 21. Mycological cure over time for pezadeftide and vehicle-treated nails.



Source: *HXL, Wilsons*

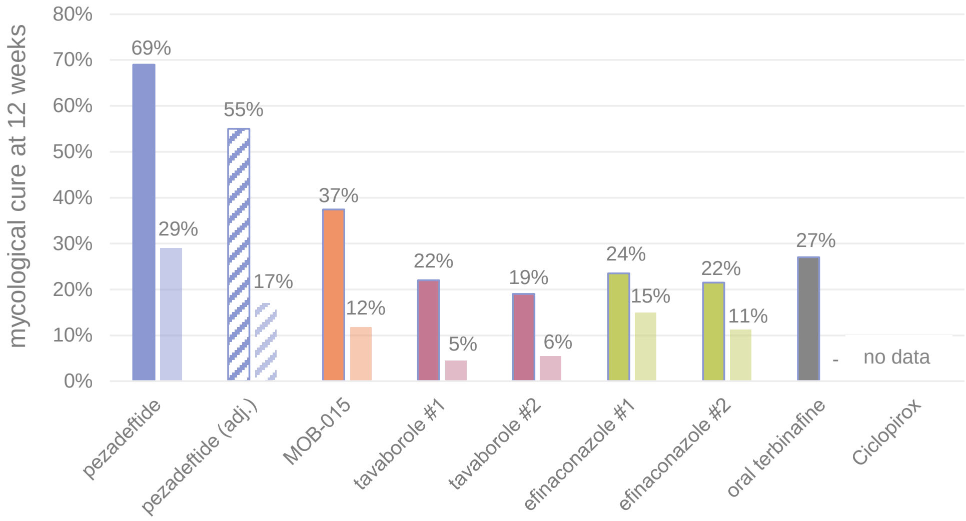
Figure 22. Mycological cure stain and culture results at 12 weeks (6 weeks' daily treatment).



Source: *HXL, Wilsons*

Comparisons with other onychomycosis agents. Noting the difficulties and caveats with cross-trial comparisons, we provide a summary of published, 12-week mycological cure rates for JUBLIA (efinaconazole 10%), KERYDIN (tavaborole 5%), PENLAC (ciclopirox 8%), LAMISIL (oral terbinafine) and the investigational agent MOB-015 (topical terbinafine). Note that all comparator results below in **Figure 23** were generated from 12 weeks' daily treatment versus 6 weeks' treatment for pezadeftide (data from cohort 4 only). Comparator data has been sourced or interpolated from large (Phase III or similar) studies that treated nails for 48 weeks followed by a 4-week treatment-free interval (52 weeks in all). Comparator studies were reasonably consistent with respect to inclusion criteria, enrolling patients with mild to moderate nature of the onychomycosis at study entry. The definition of mycological cure is also standardised across trials. In **Figure 23** we have provided two analyses for pezadeftide: a) the company reported rate of 69% based on all patients with a positive mycological result at screening; b) an adjusted rate of 55%, if patients with a mycological cure at baseline are excluded from the analysis. Note, that even on this adjusted basis, the mycological cure rate of pezadeftide is approximately twice that of all approved agents including oral terbinafine.

Figure 23. 12-week mycological cure data for pezadeftide and a selection of approved and investigational agents (active and vehicle-only controls where available). Data presented for active (left hand bar) and vehicle (right hand bar) arms.

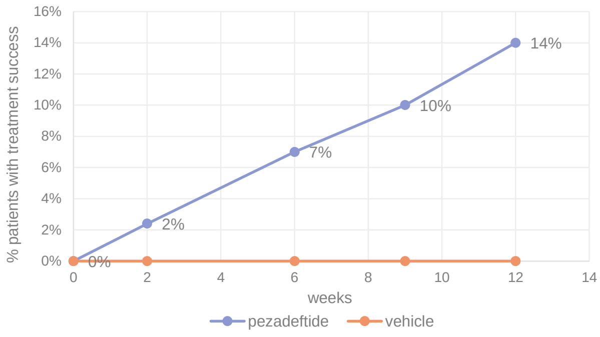


Source: *clinicaltrials.gov, Wilsons*

Clinical efficacy

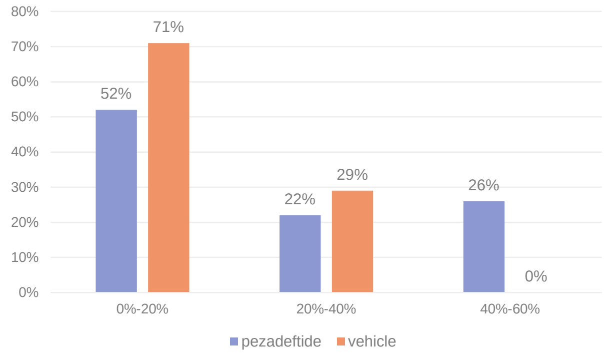
Data. Clinical efficacy is a popular secondary endpoint in onychomycosis trials defined as <10% clinical involvement of the target toenail. In the clinic this is typically assessed by photography with the surface area of the target nails calculated using imaging software. For the pezadeftide-treated group, 14% of nails achieved this endpoint at 12 weeks compared to 0% in the vehicle-treated group (**Figure 24**). The mean decrease in infected nail area was 5% for pezadeftide-treated nails compared to 3% for vehicle-treated nails (**Figure 25**). The proportion of nails that showed a greater than 40% reduction in the infected nail area (as a percentage of the baseline infected area) was substantially higher in the pezadeftide-treated group (26%) compared to vehicle (0%) (**Figure 25**).

Figure 24. Clinical efficacy over time for pezadeftide and vehicle-treated nails.



Source: HXL, Wilsons

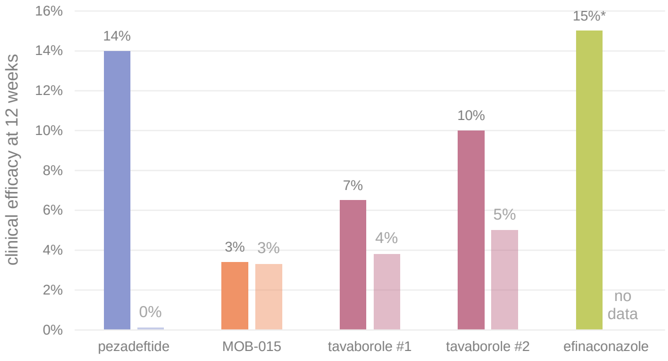
Figure 25. Reduction in infected nail area as a percentage of baseline at 12 weeks' follow up.



Source: HXL, Wilsons

Comparisons with other onychomycosis agents. In **Figure26** we provide a summary of published, 12-week clinical efficacy results for JUBLIA (efinaconazole 10%), KERYDIN (tavaborole 5%), PENLAC (ciclopirox 8%) and the investigational agent MOB-015 (topical terbinafine). Note that all comparator results below in **Figure 26** were generated from 12 weeks' daily treatment versus 6 weeks' treatment for pezadeftide (data from cohort 4 only). Comparator data has been sourced or interpolated from large (Phase III or similar) studies that treated nails for 48 weeks followed by a 4 week treatment-free interval (52 weeks in all) with the exception of efinaconazole. We are encouraged by both the absolute result at 12 weeks and by the delta from vehicle-only treatment.

Figure 26. 12-week clinical efficacy data for pezadeftide and a selection of approved and investigational agents (active and vehicle-only controls where available). Data presented for active (left hand bar) and vehicle (right hand bar) arms.



** Data sourced from a single-arm (not vehicle controlled) study in target nails with 20%-50% clinical involvement at study entry[44].*
Source: *clinicaltrials.gov, Wilsons*

[44] Iozumi, K. et al. (2019) *Efficacy of long-term treatment with efinaconazole 10% solution in patients with onychomycosis, including severe cases: a multicentre, single-arm study.* J. Dermatology 46: 641 – 651.

Summary

The Phase I/IIA HXP124-ONY-001 trial demonstrated encouraging early safety and efficacy after only 6 weeks' daily treatment with pezadeftide. The mycological cure rate of 69% is more than threefold that of efinaconazole (~23%) at 12-weeks follow-up, noting that there is no correlation between 12-week mycological cure rates and complete cure at 52 weeks[45]. Phase IIB development was warranted investigating three dosing strategies at 2.0% pezadeftide dose based on this initial dataset.

A2.2.2 Phase IIB trial (HXP124-ONY-002)

Hexima has enrolled 132 subjects in a Phase IIB, randomised, double-blinded, vehicle-controlled clinical trial[46]. The trial examines three dosing strategies using 2.0% pezadeftide versus vehicle.

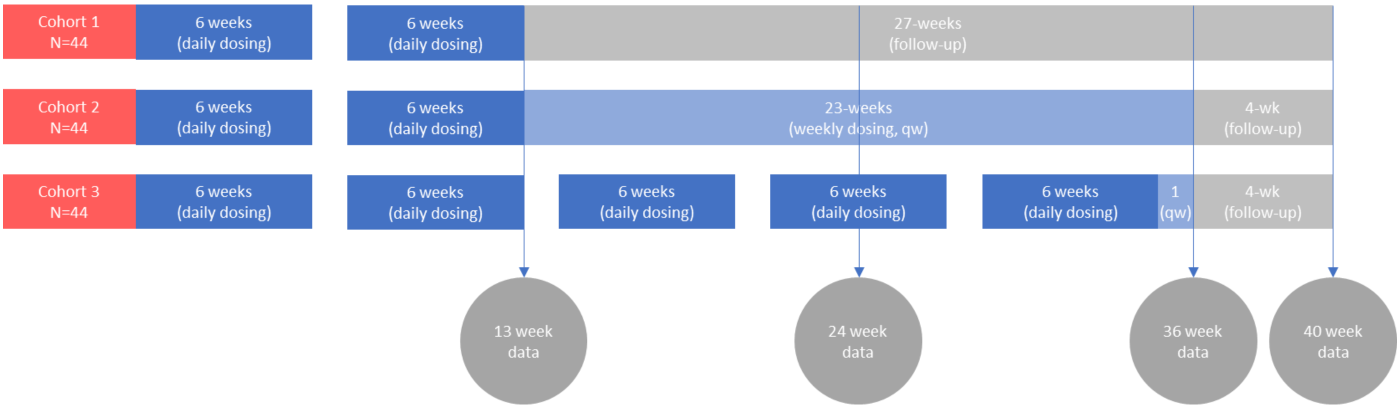
Trial design

HXP124-ONY-002 is a Phase IIB, randomised, double-blind, vehicle-controlled study in healthy volunteers with mild-to-moderate onychomycosis (ANZCTR registration number: ACTRN12620000697987)[47]. To be eligible for this study, participants had to be otherwise healthy, aged 18 to 65 years, with onychomycosis confirmed by mycological staining and/or culture. The onychomycosis needed to affect at least 20% but not more than 50% of one (or both) great toenail(s) as determined by visual inspection after the nail had been trimmed. Note this is a narrowed (milder) selection criterion than in Phase I/IIA (20%-70%).

The study entails three dose cohorts:

- **Cohort 1**. 2 x 6 week once daily treatment with pezadeftide or vehicle. Each treatment period will be separated by a 1-week washout period. Treatment periods end in a 27-week treatment-free follow up period.
- **Cohort 2**. 2 x 6 week once daily treatment separated by a 1-week washout period plus 1 x 23 week once weekly treatment with pezadeftide or vehicle. Treatment periods end in a 4-week treatment-free follow up period.
- **Cohort 3**. 5 x 6 week once-daily treatment followed by 1 x 1 week once-daily treatment with pezadeftide or vehicle. Treatment periods end in a 4-week treatment-free follow up period.

Figure 27. Phase IIB trial design. All cohorts randomised 2:1 (2.0% pezadeftide : vehicle). Note that a one week, treatment-free wash-out period separates all planned 6-week daily treatment intervals.



Source: Hexima, Wilsons

[45] Both MOB-015 and tavaborole achieved as good or better mycological cures at 12 weeks compared to efinaconazole but went on to produce materially lower complete cure rates.
[46] https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379733
[47] https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374039

Primary endpoint: to evaluate the safety and tolerability of 2.0% topical pezadeftide in treated participants with mild to moderate onychomycosis of the target great toenail. Safety and tolerability will be assessed by:

- incidence, nature, and severity of adverse events (AEs);
- incidence of treatment discontinuations due to AEs;
- changes in clinical laboratory tests from baseline over time;
- incidence of treatment emergent abnormal laboratory tests;
- physical examination abnormalities including incidence of application site reactions (burning/stinging, induration/edema, oozing/crusting, pruritis, erythema, pain and local irritation);
- changes in vital signs (systolic and diastolic blood pressures, respiratory rate, heart rate and body temperature) and 12-lead ECGs.

Secondary endpoints to be assessed at 13, 24, 36 and 40 weeks:

- mycological cure;
- complete or almost complete cure (mycological cure AND clinical involvement of ≤5% for the target great toenail);
- clinical efficacy defined as ≤10% clinical involvement;
- complete cure defined as 100% clear nail surface areas in addition to both a negative microscopy stain and negative fungal culture;
- a change in clear nail surface of ≥20% from baseline.

Clinical milestones and interpretation

Results expected 2Q 2022. Hexima's Phase IIB study involved 15 sites in Australia and New Zealand. Recruitment closed towards the end of July and top-line results are expected in the second quarter of 2022 (40-week total treatment and follow-up period for all cohorts). This study is the last planned RCT prior to initiating a Phase III campaign in 3Q 2022.

Cohorts 1-3 in descending order of commercial attractiveness. Long courses of treatment have proven challenging in both clinical trial and real-world treatment contexts[48]. Phase IIB is seeking to establish a shorter treatment interval than has ever been achieved using topicals which would bring that category into line with oral agents. Cohort 1 aims to achieve a curative result in just 12 weeks of treatment. Cohort 2 represents a middle ground: an initial, intense 12-week treatment phase followed by weekly applications out to week 40. The last cohort is closer to conventional, long course therapy (36 weeks of daily treatment).

---

[48] Gupta, A. K. et al. (2016) New *antifungal agents and new formulations against dermatophytes* Mycopathologia 182: 127 – 141.

Clinical benchmarking

In Table 13 below we summarise key efficacy and safety data from Phase III, randomised, vehicle-controlled trials for comparative topical agents. Efinaconazole remains the most efficacious approved drug with complete cure rates in the mid-teens (%). Agents have been approved with just single digit efficacy.

Table 13. Summary results from randomised, vehicle-controlled clinical trials for comparative topical agents

Agent	terbinafine (10% topical) MOB-015[49]	tavaborole 5%[50]		efinaconazole 10%[51]		ciclopirox 8%[52]	
Study	NCT02859519	NCT01270971	NCT01302119	NCT01008033	NCT01007708	Study 312	Study 313
Phase	III	III	III	III	III	III	III
Tx [follow-up] wks	48 [52]	48 [52]	48 [52]	48 [52]	48 [52]	48 [52]	48 [52]
N; Active [vehicle]	246 [119]	399 [194]	396 [205]	575 [187]	575 [187]	110 [109]	118 [117]
Demographics	84.1% male	81.2% male	81.6% male	74.5% male	80.0% male	No data	No data
Median age	55 yrs	53 yrs	55 yrs	54 yrs	52 yrs	No data	No data
Nail involvement [inclusion range]	NR† [20%-60%]	NR [20%-60%]	NR [20%-60%]	36.7% [20%-50%]	36.2% [20%-50%]	NR [20%-65%]	NR [20%-65%]
Complete cure; Active [vehicle]	**4.5% [0.0%]***	**6.5% [0.5%]***	**9.1% [1.5%]***	**17.8% [3.3%]***	**15.2% [5.5%]***	**5.5% [0.9%]***	**8.5% [0.0%]***
Mycological cure; Active [vehicle]	69.9% [27.7%]*	31.1% [7.2%]*	35.9% [12.2%]*	55.2% [16.8%]*	53.4% [16.9%]*	28.6% [13.3%]*	34.5% [8.8%]*
Clinical efficacy; Active [vehicle]	19.1% [8.4%]	26.1% [9.3%]*	27.5% [14.6%]*	35.7% [11.7%]*	31.0% [11.9%]*	No data	No data
AEs; Active [vehicle]	47.2% [51.3%]	64.4% {69.9%]	57.5% [54.0%]	66.0% [64.5%]	61.0% [58.5%]	No data	No data
Disc AEs; Active [vehicle]	2.8% [4.2%]	0.3% [1.0%]	0.5% [0.5%]	3.2% [0.5%]	1.9% [0.0%]	No data	No data

Complete cure defined as 0% clinical involvement of the target toenail and mycological cure.

Mycological cure defined as negative potassium hydroxide examination and negative fungal culture of target toenail samples.

Clinical efficacy defined as <10% clinical involvement of target toenail.

NR – data not reported

***** denotes a statistically significant result

† In the MOB-015 Phase III trial median clinical involvement at baseline was not reported but 79.7% patients had toenail involvement of ≥25% to ≤50%.

Moberg's European Phase III trial for MOB-015 was a non-inferiority design versus 8% ciclopirox (MICLAST). Study enrolled 452 patients. Complete cure of target toenails at 52 weeks was achieved in 1.8% of patients receiving MOB-015 and in 1.6% of patients receiving ciclopirox. Mycological cure was achieved in 84% percent of patients for MOB-015, superior to 42% for ciclopirox. Treatment success (mycological cure and almost or completely clear great toenail) was reached for 21.9% of the MOB-015 patients versus 18.9% in the ciclopirox group. The study confirmed early onset of action with 46% of patients mycologically cured at 12 weeks.

[49] Gupta. A. K. et al. (2020) *Efficacy and safety of topical terbinafine 10% solution (MOB-015) in the treatment of mild-to-moderate distal subungual onychomycosis: A randomized, multi-center, double-blind, vehicle-controlled phase 3 study* J. Am. Acad. Dermatology https://doi.org/10.1016/j.jaad.2020.06.055

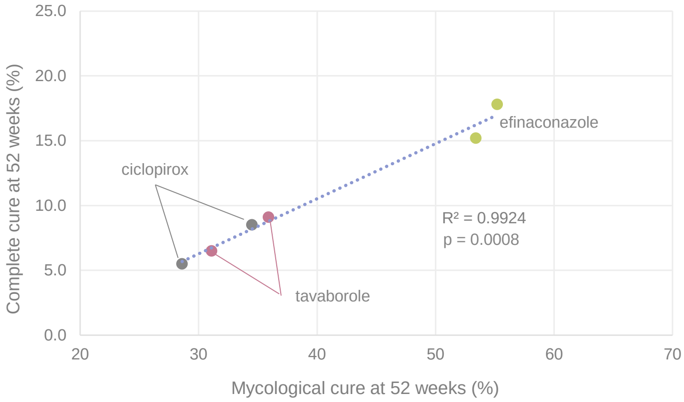
[50] Elewski, B. E. et al. (2015) *Efficacy and safety of tavaborole topical solution 5% a novel boron-based antifungal agent for the treatment of toenail onychomycosis: results from 2 randomised Phase III studies* J. Am. Acad. Dermatology 73: 62 – 69.

[51] Elewski, B. E. et al. (2013) *Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies* J. Am. Acad. Dermatology http://dx.doi.org/10.1016/j.jaad.2012.10.013

[52] Aventis Pharma. Penlac monograph. df.hres.ca/dpd_pm/00015736.pdf

Correlation between mycological and complete cure rates in Phase III trials. In **Figure 28** we plot 52-week mycological and complete cure rates (efinaconazole, tavaborole and ciclopirox) against one another and observe a correlation. Intuitively this makes sense as one expects the eradication of hyphae in the nail bed should allow growth of the uninfected, visually clear nail. If Hexima's Phase IIB confirms mycological cure ≥ 70% then the correlation suggests a complete cure rate of ≥20% may be achievable. A caveat to consider before jumping to that conclusion is to consider Moberg's MOB-015 program which we have not plotted below but would be a dramatic outlier. MOB-015 achieved mycological cures of 70%-84% in Phase III trials at 52 weeks yet only saw complete cure rates of 1.8% to 4.5%. The reason for this is unknown but anecdotally, the vehicle used in that formulation may have discoloured the nail. As complete cure is judged using digital photography and image analysis, this discolouration may have obscured the results.

Figure 28. Complete and mycological cure data measured in Phase III RCTs suggest a convincing correlation (R^2 = 0.99; p-value = 0.0008).



Source: Wilsons

A2.3 Phase III campaign considerations/assumptions

Two randomised, multicentre, vehicle-controlled Phase III trials to enrol approximately 800-1,1000 patients. Complete cure at 52 weeks is the established predicate for approval in this indication. Two identical Phase III studies constitute the minimum, but sufficient, evidentiary basis for approval with that precedent set by efinaconazole, terbinafine, tavaborole and ciclopirox. We would expect inclusion and exclusion criteria to resemble those chosen for the Phase IIB: adult subjects with mild to moderate disease. Onychomycosis trials also often exclude patients with excessively thick nail plates (> 3mm) or with comorbidities including uncontrolled diabetes, peripheral circulatory insufficiency or immunodeficiency.

Secondary efficacy endpoints. Key secondary efficacy measures are likely to include:

- Mycological cure at week 52 (negative direct KOH microscopy AND negative fungal culture of dermatophytes of the nail). Note that the gold standard definition of KOH microscopy and fungal culture is controversial. KOH staining has a false negative rate ranging from 5%-15% and may lead to false positive efficacy signals because live fungal cells are indistinguishable from dead ones[15]. Fungal cultures take up to four weeks to yield results and are associated with 30%-57% sensitivity[53]. Hexima's Phase III is likely to retain gold standard analytical approaches to assist benchmarking versus other agents.
- Complete or almost complete cure (defined as ≤5% but ≥0% infection in the target nail using digital assessment) AND mycological cure.
- Clinical efficacy defined as 0% to ≤10% area of infection.
- A change in clear nail surface area ≥20% from baseline.

Sample size. Individual registration studies to date have recruited up to 762 patients each (efinaconazole) but as few as 220 (ciclopirox). Ultimately this will be informed by the efficacy signals observed in Phase IIB and the dosing strategy selected for Phase III development. 2:1 randomisation is common. Given the long treatment and follow-up phase, trial sizing often anticipates and accommodates drop-out rates of 20%.

Safety endpoints. Similar safety and tolerability analyses to those in Phase IIB:

- incidence and severity of AEs and SAEs;
- treatment discontinuations;
- changes in clinical laboratory tests from baseline over time;
- incidence of treatment emergent abnormal laboratory tests;
- incidence of application site reactions (burning/stinging, induration/oedema, oozing/crusting, pruritis, erythema, pain and local irritation);
- changes in vital signs (systolic and diastolic blood pressures, respiratory rate, heart rate and body temperature) and 12-lead ECGs;
- pharmacokinetic and/or pharmacodynamic parameters.

[53] Gustafson, E. *et al.* (2019) *DNA-based detection for onychomycosis correlates better to histopathology than does fungal culture*. Dermatol. Online J. 15: 25 – 27.

A2.4 Competitive development situation

The drug development landscape for onychomycosis is sparse with only a few antimicrobial peptides and terbinafine reformulations in active development. Scottish biotech Novabiotics' NP213 program was of interest given that it shares some characteristics of pezadeftide (small, water soluble peptide). The company had early commercial success in partnering with Taro Pharmaceuticals in the USA. Phase IIa trials revealed very low mycological cures after 180 days follow up[54]. We understand that Taro undertook a Phase IIB study but reported that the trial "did not meet the main goal" and returned the rights to Novabiotics. Novabiotics has subsequently licensed rights to Japanese and European partners but likely as an OTC product through on-line or retail channels. Our view is that NP213 is unlikely to be developed as a prescription pharmaceutical in any major market. Reformulation is a common strategy in this indication recalling Mayne Pharma's oral SUBA-itraconazole program[55] and referencing ciclopirox and terbinafine projects in **Table 14**. Reformulated ciclopirox (P-3051) is widely available in Europe but was never developed for the US market. The same formulation approach was tried by Almirall with terbinafine but detailed data was never published and the planned US Phase III study withdrawn. We understand that this may be released as an OTC product in Europe although the product's licensing status is unclear. Swedish developer Moberg completed two Phase III trials with their proprietary formulation (MOB-015) but achieved very low complete cure rates (<5%). Blueberry Therapeutics (Manchester, UK) is recruiting a Phase IIB for another terbinafine variant but have not disclosed data from its prior Phase I/II trials. Mycovia has produced interesting Phase II results with VT-1161 (oteseconazole) but seems to be pressing ahead with acute vulvovaginal candidiasis as preferred Phase III indication.

Table 14. Other investigational assets in development for onychomycosis

Asset	Company	Agent	Development stage	Results	Trial identifier
MOB-015	Moberg Pharma	Terbinafine 10% topical solution	Phase III	Complete cure of 1.8% to 4.5% after 48 weeks daily treatment (52 week follow up). Mycological cures of 70%-84%.	NCT02859519 NCT02866032
P-3058	Almirall	Terbinafine 10% topical solution in hydroxypropyl chitosan (HPCH)	Phase III	Almirall halted the development of P-3058 in USA but completed a Phase III in Europe. 953 patients randomised to P-3058, its vehicle, or amorolfine 5% nail lacquer. Complete cure rate was not disclosed[56].	NCT02547701 NCT03094468 (withdrawn)
P-3051	Various	Ciclopirox 8% in HCPH	Not developed for USA. Marketed in various countries as Ciclopoli, Fulcare, Kitonail, Myconail.	467 patients treated once daily for 48 weeks with 12-week follow-up. Complete cure rate of 7.6% at 60 weeks[57].	n/a
BB2603	Blueberry Therapeutics	Terbinafine topical spray	Phase IIB recruiting now under an FDA Investigational New Drug approval.	Single centre Phase I/II enrolled 46 patients confirmed safety with no systemic drug exposure. Trial evaluated clinical improvement at 52 weeks but efficacy results are not published[58].	NCT04188574
NP213	Novabiotics	Synthetic cyclic peptide	Phase IIA, Phase IIB	Phase IIA. Mycological cure of 13.3% of all patients and 23.1% in mind-moderate patients at 180 days follow-up. Drug applied daily for 28 days in both Phase IIA studies.	EudraCT 2008-001496-29 NCT02343627
KP-607	Kaken Pharmaceutical	Unknown novel topical agent	Phase II	No results. Previously a collaboration with Bausch Health Care (terminated). Referred to in Kaken's 1Q21 presentation.	n/a
VT-1161	Mycovia Pharmaceuticals	Oteseconazole Oral tablets	Phase II	Phase II examined 2 weeks daily followed by 10 and 22 weeks weekly dosing. Complete cure rates of 32%-42% versus 0% placebo[59].	NCT02267356

Source: Company information, clinicaltrials.gov, Wilsons

[54] Mercer, D. K. et al. (2020) *NP213 (Novexatin): a unique therapy candidate for onychomycosis with a differentiated safety and efficacy profile* Medical Mycology 58: 1064 – 1072.
[55] SUBA-itraconazole was launched in Europe and Australia as the branded product LOZANOC. Mayne Pharma did not pursue an onychomycosis indication in the USA and launched the product as TOLSURA for the treatment of systemic infections.
[56] See: https://www.almirall.it/documents/portlet_file_entry/4257831/181712_PM1331_ALMIRALL_ENG_v3.pdf/445217e7-2d57-4119-8101-aa147f0897f1
[57] Piraccini, B. M. and Tosti, A. (2019) *Ciclopirox hydroxypropyl chitosan: efficacy in mild to moderate onychomycosis* Skin Appendage Disord. 5: 13 – 19.
[58] See: https://www.clinicaltrialsarena.com/news/blueberry-reports-positive-results/
[59] Elewski, B. et al. (2021) *A Phase II randomised, double-blind, placebo-controlled, dose ranging study to evaluate the efficacy and safety of VT-1161 oral tablets in the treatment of patients with distal and lateral subungual onychomycosis of the toenail* Br. J. Dermatol. 184: 270 – 280.

A3. Intellectual Property

Hexima owns 14 patent families which provides comprehensive coverage of defensin proteins, nucleic acids encoding them and their use. In Table 15 below we summarise the most important patents relating to pezadeftide and its use. Hexima owns additional patents in the field of crop protection with both anti-fungal and insecticidal function (not reviewed).

Table 15. Selected patents owned by Hexima

Indication/methodology	Granted US Patents	Ownership	Filing date	Jurisdictional notes
A method of treatment	US 10,973,874 US 10,010,576 US 9,713,632	Hexima	May 29 2015	Ref: WO/2016/061619 Granted: Europe, China, Mexico, Singapore. Pending: Australia, Canada, Japan, Serbia, Korea.
	Summary: These patents are central to the immediate investment case for pezadeftide, protecting topical pharmaceutical compositions comprising plant defensins of specified structures. The claims describe both specific defensin protein sequences and more broadly defined ‘consensus’ structures. This patent family also includes ‘method of use’ claims, specific to onychomycosis. The method claims also capture combinations of plant defensins with other anti-fungal drugs. Finally, there are claims that restrict the types of excipients used in formulating defensins.			
Agents and methods of treatment	US 10,568,930	Hexima	24 Oct 2016	Ref: WO/2015/161348 Granted: USA, Australia. Pending: Canada, India, Japan. Withdrawn: Europe
	Summary: A method patent describing the combination of plant defensins and a β-glucan synthase inhibitor (including capsofungin[60]). Claims cover specific fungal pathogens and is not limited to topical application.			
Agents and methods of treatment of pathogens	US 10,231,450	Hexima	24 Oct 2016	Ref: WO 2015/161346 Granted: USA, Australia. Pending: India, Canada, Japan. Withdrawn: Europe
	Summary: A method patent for inhibiting growth, infection or infestation using a combination of permeabilising defensin and engineered defensins (comprising Class I and II elements) and a non-defensin peptide. Claims cover topical application of these combinations to humans, animals and plants.			
Antipathogenic methods	US 10,357,536 US 9,943,564	Hexima	22 Nov 2013	Ref: WO 2014/078900 Granted: USA, Australia, Europe. Pending: Canada, Japan.
	Summary: A method patent describing the inhibition of fungal infection (prophylactically) using a combination of Class I defensin and a permeabilising defensin with specific structures. The scope of the patent covers human and non-human animal use but most of the examples and most detailed claims pertain to crop protection.			

Source: Wilsons

[60] Capsofungin belongs to a class of anti-fungal drugs known as echinocandins which inhibit the glucan components of fungal cell walls.

A4. Board and management

A4.1 Board

Professor Jonathan West – Non-executive Chairman

Professor Jonathan West is the Director of the Australian Innovation Research Centre. Prior to assuming his current appointment, he taught for 18 years at the Harvard University Graduate School of Business Administration, where he was Associate Professor, founding Director of the Harvard University Life Sciences Initiative, and from 1998-1999 the Novartis Faculty Research Fellow. He has been Visiting Professor at Hitotsubashi University and the Nomura School of Advanced Management in Tokyo, Japan and Visiting Professor at the University de Paris IX-Dauphine, Sorbonne. Professor West was Chairman of the Asia Advisory Council of Bunge Ltd, one of the world's largest agribusiness processing and trading companies, and has served as an advisor to other major corporations and several Governments around the world, including in the life sciences field, DuPont, Roche, Novartis, Syngenta and the J.R. Simplot Company, along with the Governments of Singapore, Japan, Hong Kong and France.

Michael Aldridge – Managing Director

Mr Aldridge most recently served as Senior Vice President, Corporate & Strategic Development of Codexis from October 2016 until August 2018. Prior to that, from January 2012 to September 2014, Mr. Aldridge served as Senior Vice President, Corporate Strategic Development for Questcor Pharmaceuticals, Inc., a publicly-traded biopharmaceutical company acquired by Mallinckrodt Pharmaceuticals in 2014. From May 2010 to September 2012, Mr. Aldridge served as Chief Executive Officer and a member of the board of directors for Xenome Limited, a privately-held biopharmaceutical company headquartered in Australia. Between 2003 and 2009, Mr. Aldridge served as Chief Executive Officer and a member of the board of directors and a strategic consultant of Peplin, Inc., a publicly-traded drug development company acquired by LEO Pharma A/S in 2009.

Dr Nicole van der Weerden – Executive Director

Dr Nicole van der Weerden completed her PhD in Biochemistry at La Trobe University in 2007. Her PhD research on the antifungal properties and mechanism of action of plant defensins led to the award of a prestigious Victoria Fellowship in 2006. Since completing her PhD, Nicole has worked for Hexima Limited and has led the gene discovery program for the Pioneer partnership on control of fungal diseases in corn. Nicole has completed an MBA at Melbourne Business School.

Justin Yap – Non-executive Director

Mr Yap is a Non-Executive Director of CathRx Limited, an Australian medical device company commercialising cardiac electrophysiology catheters for the treatment of heart rhythm disorders. He is a Non-Executive Director of Wilhelm Integrated Solutions Pty Ltd, a distributor of integrated operating room technology to hospitals around Australia. Prior to this, he began his career in investment banking for Mosaic Risk Management Pty Ltd, a wholly owned subsidiary of Wilson HTM Limited specialising in derivatives risk management.

Scott Robertson – Non-executive Director

Mr. Robertson is currently Chief Financial Officer at DiCE Molecules. Prior to DiCE Molecules, Mr. Robertson served at DuPont where he was Business Development Director for DuPont Pioneer with responsibility for the business unit's crop genetics and precision agriculture M&A activity. He also held the position of portfolio manager with DuPont Ventures where he focused on strategic investment opportunities in production agriculture and the intersection of agriculture and downstream renewable technologies. Prior to joining DuPont, Mr. Robertson was an investment professional at MPM Capital, a life sciences-dedicated venture capital fund, and previous to that a member of the Healthcare Investment Banking groups at Merrill Lynch & Co. and Thomas Weisel Partners. He received a Bachelor of Science in Business Administration from the University of Southern California and an M.B.A. from the Haas School of Business at the University of California, Berkeley.

Jake Nunn – Non-executive Director

Based in Menlo Park, CA, Jake Nunn has more than 25 years' experience in the life science industry as an investor, independent director, research analyst and investment banker. Jake is currently a venture advisor at New Enterprise Associates (NEA), where he was a partner from 2006 to 2018. Jake is a Director of Addex Therapeutics (SIX,Nasdaq: ADXN), Oventus Medical (ASX: OVN), Regulus Therapeutics (Nasdaq: RGLS) and Trevena, Inc. (Nasdaq: TRVN). He was a previous Director of several companies in the pharmaceutical sector including Dermira Inc. (acquired by Eli Lilly) and Hyperion Therapeutics (acquired by Horizon Pharma plc), and a board observer at Vertiflex, Inc. (acquired by Boston Scientific). Prior to NEA, Jake was a Partner specializing in life sciences investing at MPM Capital. Previously, he was a healthcare research analyst and portfolio manager at Franklin Templeton Investments and an investment banker with Alex. Brown & Sons. Jake received an MBA from the Stanford Graduate School of Business and an AB in Economics from Dartmouth College. Jake holds the Chartered Financial Analyst designation, is a member of the CFA Society of San Francisco, and recently completed the Stanford GSB Directors' Consortium executive education program.

A4.2 Management

Michael Aldridge – Chief Executive Officer

As above.

Dr Nicole van der Weerden – Chief Operating Officer

As above.

Dr Nancy Sacco – Chief Development Officer

Dr Sacco brings over 20 years of experience in the pharmaceutical industry including non-clinical discovery, late-stage clinical development, registration, and approval of pharmaceutical products. Dr Sacco holds a PhD from West Virginia University School of Medicine. Prior to this appointment, Dr Sacco held Vice President and Head of Clinical Development roles at Xentria, Inc. and AnaptysBio, Inc., overseeing programs with monoclonal antibodies for rare and dermatologic diseases. In addition, Dr Sacco held executive leadership positions at Revance Therapeutics, Inc. and Avexis, Inc (now Novartis), overseeing clinical operations including the initiation and completion of pivotal studies evaluating safety and efficacy of innovative products (proprietary neurotoxin Daxibotulinum and AVV9 gene therapy ZolgenSMA, respectively).

Professor Marilyn Anderson – Chief Science Officer

Professor Anderson is a founding scientist of Hexima. She has over 30 years' experience in scientific research in the area of plant biochemistry and genetics. She is a Professor of Biochemistry at La Trobe University and a Member of the Australian Academy of Science Council. She was appointed Hexima's Chief Science Officer in July 2009. Professor Anderson was a director at South East Water Limited for over 10 years prior to her appointment to the board of City West Water in 2008. She is a Fellow of the Australian Academy of Science, of the Australian Academy of Technological Sciences and Engineering and of the Australian Institute of Company Directors.

Helen Molloy – Financial Controller

Helen Molloy holds a Bachelor of Business from Federation University, and is a member of the Australian Society of Certified Practicing Accountants. Helen has previously worked as a financial accountant within the Treasury department of the Mayne Group, as well as with Orica Chemicals and Incitec Pivot Limited. Helen has been the Financial Controller for Hexima for 10 years and was appointed sole Company secretary for the Group in November 2019.

Dr Susanna Herd – IP Manager

Dr Susanna Herd holds a PhD, a Dip Ed and a Master of Intellectual Property Law from the University of Melbourne. Her research interests have included inherited disorders of copper metabolism and the role of molecular chaperones in the folding of proteins in mitochondria. She held the position of Lecturer in the Department of Biochemistry at La Trobe University until 2005 when she joined Hexima as Intellectual Property Manager. She has extensive experience in the management of Hexima's patent portfolio, including the preparation and prosecution of patents and the development of IP strategy. Dr Herd is a member of the Hexima Limited Institutional Biosafety Committee.

Hexima Limited (HXL)

Business description

Hexima (HXL:ASX) is a clinical stage Australian biopharma developing a novel class of plant-derived antimicrobial peptides called defensins. Hexima's lead asset, pezadeftide, is the subject of a Phase IIB clinical trial treating onychomycosis.

Investment thesis

We initiate coverage on Hexima with an OVERWEIGHT rating and a risked price target of $0.75 per share. Hexima has been reborn as an ASX-listed entity. This iteration explores the pharmaceutical value of plant-derived, antifungal 'defensin' biology, having abandoned earlier agricultural pursuits in crop protection. Lead asset pezadeftide has achieved promising early clinical results treating deep seated fungal infections of the toenail (onychomycosis) as a topical medication. Pezadeftide is a water-soluble agent that penetrates nails rapidly, devastates the fungal pathogens in the nail bed and allows healthy nail regrowth. Our thesis is that the availability of an efficacious, pragmatically priced, short-course treatment option can create a mini-blockbuster in dermatology. We assess US$285M peak sales in US and Japan. Pezadeftide's novel mechanism of action makes it a logical candidate for investigation in other poorly served anti-fungal markets.

Revenue drivers

Regulatory approvals and product launches

Commercial payments from licensing transactions

R&D tax rebates and other grant funding

Balance sheet

Net cash of $3.4M as at June 30, 2021.

Margin drivers

Low cost of goods drives ~95% gross margin at forecast ASP

SG&A investment levels

Milestone and royalties have minimal costs attached.

Board

Professor Jonathan West – Chairman

Michael Aldridge – Executive Director

Dr Nicole van der Weerden – Executive Director

Justin Yap – Non-executive Director

Scott Robertson – Non-executive Director

Jake Nunn – Non-executive Director

Helen Molloy – Company Secretary

Key issues/catalysts

Clinical trial results

Regulatory interactions with EMA and FDA

Competitor development progress

Indication expansion opportunities

Management

Michael Aldridge – CEO

Dr Nicole van der Weerden – COO

Dr Nancy Sacco – Chief Development Officer

Professor Marilyn Anderson – CSO

Risk to view

Clinical trial failures or delays

Unsuccessful licensing activities

Access to development capital

Contact details

Hexima Limited | La Trobe Institute for Molecular Science
Level 4, LIMS2
La Trobe University VIC 3086
Australia

Disclaimers and Disclosures

Recommendation structure and other definitions

Definitions at wilsonsadvisory.com.au/disclosures.

Analyst certification

Each analyst of Wilsons Advisory and Stockbroking Limited (ACN 010 529 665: AFSL 238375) ("Wilsons") whose name appears in this research certifies that (1) the recommendations and opinions expressed in this research accurately reflect the analyst's personal, independent and objective views about any and all of the subject securities or issuers; (2) no part of the analyst's compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed by the analyst in the research; and (3) to the best of the analyst's knowledge, he/she is not in receipt of material non-public information about the issuer.

Disclaimer

This document has been prepared by Wilsons. This communication is not to be disclosed in whole or part or used by any other party without Wilsons' prior written consent. All material presented in this document, unless specifically indicated otherwise, is under copyright to Wilsons. None of the material, its content, nor any copy of it, may be altered in any way, transmitted to, copied or distributed to any other party, without the prior express written permission of Wilsons. This document is not directed to, or intended for distribution to or use by, any person or entity who is a citizen or resident of or located in any locality, state, country or other jurisdiction where such distribution, publication, availability or use would be contrary to law or regulation or which would subject Wilsons to any registration or licensing requirement within such jurisdiction.

This document is being supplied to you solely for your information and no action should be taken on the basis of or in reliance on this document. To the extent that any information prepared by Wilsons contains any financial product advice, it is general advice only and has been prepared by Wilsons without reference to your objectives, financial situation or needs. You should consider the appropriateness of the advice in light of your own objectives, financial situation and needs before following or relying on the advice. You should also obtain a copy of, and consider, any relevant disclosure document before making any decision to acquire a financial product. Please refer to Wilsons' Financial Services Guide for more information: wilsonsadvisory.com.au/disclosures. Any person, before acting on any advice contained within this communication, should first consult with a Wilsons investment adviser to assess whether the advice within this communication is appropriate for their objectives, financial situation and needs. Those acting upon such information without advice do so entirely at their own risk.

This document provided by Wilsons is current as at the date of the issue but may be superseded by future publications. Wilsons assumes no obligation to update the information or advise on further developments relating to the company or companies covered in this document ("Companies") or relevant financial products. Wilsons has not independently verified all of the information given in this document which is provided at a point in time and may not contain all necessary information about the Companies. Wilsons makes no warranty, express or implied, concerning any information prepared by Wilsons. Wilsons expressly disclaims (1) any implied warranty of merchantability or (2) fitness for a particular purpose, including any warranty for the use or the results of the use of any information prepared by Wilsons with respect to their correctness, quality, accuracy, completeness, reliability, performance, timeliness, or continued availability. Wilsons' research content should be viewed as an additional investment resource, not as your sole source of information. To the fullest extent permitted by law Wilsons, its related bodies corporate and their respective officers, directors, employees or agents, disclaim any and all liabilities for any loss or damage howsoever arising in connection with the use of this document or its contents. Past performance does not necessarily indicate a financial product's likely future performance.

This document may contain "forward-looking statements". Forward-looking statements, opinions and estimates provided in this document are based on assumptions and contingencies which are outside the control of Wilsons and are subject to change without notice (including but not limited to economic conditions, market volatility and company-specific fundamentals), and therefore may not be realised in the future.

This report does not constitute an offer or invitation to purchase any securities and should not be relied upon in connection with any contract or commitment whatsoever.

Regulatory disclosures

Issued by Wilsons Advisory and Stockbroking Limited (Wilsons) ABN 68 010 529 665 - Australian Financial Services Licence No 238375, a participant of ASX Group and should be read in conjunction with the disclosures and disclaimer in this report. Important disclosures regarding companies that are subject of this report and an explanation of recommendations can be found at the end of this document. Wilsons Corporate Finance Limited ACN 057 547 323, AFSL 238 383 acted as Joint Lead Manager in the October 2021 Institutional Placement of Hexima Limited securities for which it received fees or will receive fees for acting in this capacity. Wilsons Advisory and Stockbroking Limited may have a conflict of interest which investors should consider before making an investment decision. Wilsons Advisory and Stockbroking Limited, Wilsons Corporate Finance Limited and its related bodies corporate trades or may trade as principal in the securities that are subject of the research report.

Wilsons contact

For more information please phone: 1300 655 015 or email: publications@wilsonsadvisory.com.au