Clinuvel Pharmaceuticals CUV.AX CUV AU

HEALTH CARE & PHARMACEUTICALS

NOMURA
EQUITY RESEARCH

Positive results from Phase IIa study

Statistically significant results – will progress to a Phase IIb

December 19, 2012

Rating Remains	**Buy**
Target price Remains	AUD 3.38
Closing price December 18, 2012	AUD 1.86
Potential upside	+81.7%

Action: Statistically significant results from its US Phase IIa study

CUV announced successful, statistically significant results from its US Phase IIa pilot study (CUV102) of its afamelanotide 16mg implant in the pigmentation disorder Vitiligo. These results show that afamelanotide in combination with narrowband UVB (NB-UVB) therapy significantly improves repigmentation of depigmented lesions in Vitiligo patients compared to NB-UVB as a single therapy. The primary study objective was achieved in that extent of repigmentation was significant in the treatment arm (p=0.025/p=0.023). From here, CUV will most likely undertake a Phase IIb trial likely to be conducted first in Europe and Asia.

Catalyst: If successful, CUV product would likely be the only branded treatment in NSV

Vitiligo is a condition that affects up to 45mn people globally. We believe the Vitiligo market is currently USD1.4bn pa, consisting of generic treatments and UVB. We believe the current lack of high-margin branded pharma treatments in the Vitiligo market could mean that, should it be approved, then CUV's afamelanotide would be of interest to established dermatology companies, because these companies have salesforces and associated infrastructure that already detail product to dermatologists.

Valuation: News in line with forecasts, TP remains AUD3.38

Starting from potential approval in 2016F, we believe that if an eventual 10% of US and EU patients were to use afamelanotide, the total CUV NSV opportunity is worth AUD7.62/share. At the current clinical stage, this translates to a risk-weighted NPV of AUD1.63/share from Vitiligo.

30 Jun	FY12		FY13F		FY14F		FY15F
Currency (AUD)	Actual	Old	New	Old	New	Old	New
Revenue (mn)	1	4	4	8	8	22	22
Reported net profit (mn)	-10	-10	-10	-8	-8	0	0
Normalised net profit (mn)	-10	-10	-10	-8	-8	0	0
FD normalised EPS	-31.75c	-29.43c	-29.43c	-21.68c	-21.68c	0.95c	0.95c
FD norm. EPS growth (%)	na	na	na	na	na	na	na
FD normalised P/E (x)	na	N/A	na	N/A	na	N/A	>100
EV/EBITDA (x)	na	N/A	na	N/A	na	N/A	na
Price/book (x)	4.1	N/A	16.4	N/A	>100	N/A	68.7
Dividend yield (%)	na	N/A	na	N/A	na	N/A	na
ROE (%)	-65.0	-119.5	-119.5	-396.4	-396.4	49.8	49.8
Net debt/equity (%)	net cash	net cash	net cash	net cash	net cash	net cash	net cash

Source: Company data, Nomura estimates

Key company data: *See page 2 for company data and detailed price/index chart.*

Anchor themes

We continue to believe that there is a very high possibility of CUV getting afamelanotide to the market. This points to cashflow from sales, and sooner than for most other biotechnology companies.

Nomura vs consensus

There are no consensus figures.

Research analysts

Australia Health Care & Pharmaceuticals

Dr David Stanton - NAL

Zara Lyons - NAL

See Appendix A-1 for analyst certification, important disclosures and the status of non-US analysts.

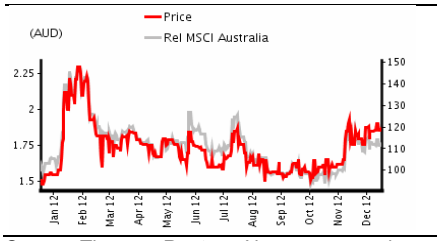
Key data on Clinuvel Pharmaceuticals

Income statement (AUDmn)

Year-end 30 Jun	FY11	FY12	FY13F	FY14F	FY15F
Revenue	**1**	**1**	**4**	**8**	**22**
Cost of goods sold	0	0	-1	-3	-8
Gross profit	**1**	**1**	**3**	**5**	**14**
SG&A	-14	-11	-13	-14	-14
Employee share expense					
Operating profit	**-13**	**-10**	**-11**	**-8**	**-1**
EBITDA	**-13**	**-10**	**-11**	**-8**	**0**
Depreciation	0	0	0	0	0
Amortisation	0	0	0	0	0
EBIT	-13	-10	-11	-8	-1
Net interest expense	1	1	1	1	1
Associates & JCEs					
Other income	0	0	0	0	0
Earnings before tax	**-11**	**-10**	**-10**	**-8**	**1**
Income tax	0	0	0	0	0
Net profit after tax	**-11**	**-10**	**-10**	**-8**	**0**
Minority interests	0	0	0	0	0
Other items					
Preferred dividends					
Normalised NPAT	**-11**	**-10**	**-10**	**-8**	**0**
Extraordinary items	0	0	0	0	0
Reported NPAT	**-11**	**-10**	**-10**	**-8**	**0**
Dividends	0	0	0	0	0
Transfer to reserves	**-11**	**-10**	**-10**	**-8**	**0**
Valuation and ratio analysis					
Reported P/E (x)	na	na	na	na	>100
Normalised P/E (x)	-4.3	-5.1	-5.5	-7.5	172.4
FD normalised P/E (x)	na	na	na	na	>100
FD normalised P/E at price target (x)	na	na	na	na	>100
Dividend yield (%)	na	na	na	na	na
Price/cashflow (x)	na	na	na	na	3.1
Price/book (x)	3.0	4.1	16.4	>100	68.7
EV/EBITDA (x)	na	na	na	na	na
EV/EBIT (x)	na	na	na	na	na
Gross margin (%)	100.0	100.0	64.8	63.7	62.6
EBITDA margin (%)	-1,205.8	-1,421.7	-254.6	-98.9	-2.2
EBIT margin (%)	-1,214.6	-1,430.3	-255.9	-99.6	-2.5
Net margin (%)	-1,096.0	-1,351.3	-242.5	-93.4	1.7
Effective tax rate (%)	na	na	na	na	30.0
Dividend payout (%)	na	na	na	na	0.0
Capex to sales (%)	6.7	0.6	2.7	1.4	0.6
Capex to depreciation (x)	0.8	0.1	2.0	2.0	2.0
ROE (%)	-53.3	-65.0	-119.5	-396.4	49.8
ROA (pretax %)	-139.9	-183.6	-187.8	-75.3	-2.3
Growth (%)					
Revenue	na	-30.6	481.7	101.1	157.4
EBITDA	na	na	na	na	na
EBIT	na	na	na	na	na
Normalised EPS	na	na	na	na	na
Normalised FDEPS	na	na	na	na	na
Per share					
Reported EPS (AUD)	-37.58c	-31.75c	-29.43c	-21.68c	0.95c
Norm EPS (AUD)	-37.58c	-31.75c	-29.43c	-21.68c	0.95c
Fully diluted norm EPS (AUD)	-37.58c	-31.75c	-29.43c	-21.68c	0.95c
Book value per share (AUD)	0.54	0.39	0.10	0.01	0.02
DPS (AUD)	0.00	0.00	0.00	0.00	0.00

Source: Company data, Nomura estimates

Relative performance chart (one year)



Source: ThomsonReuters, Nomura research

(%)	1M	3M	12M
Absolute (AUD)	0.0	-8.4	5.8
Absolute (USD)	-1.1	-3.7	3.4
Relative to index	-3.2	-14.9	3.3
Market cap (USDmn)	61.6		
Estimated free float (%)	100.0		
52-week range (AUD)	2.31/1.4		
3-mth avg daily turnover (USDmn)	0.03		

Source: Thomson Reuters, Nomura research

Notes

Revenues started for CUV in FY11

Cashflow (AUDmn)

Year-end 30 Jun	FY11	FY12	FY13F	FY14F	FY15F
EBITDA	-13	-10	-11	-8	0
Change in working capital	3	3	5	6	20
Other operating cashflow	0	-3	1	1	1
Cashflow from operations	**-9**	**-10**	**-5**	**-2**	**20**
Capital expenditure	0	0	0	0	0
Free cashflow	**-10**	**-10**	**-5**	**-2**	**20**
Reduction in investments	0	0	0	0	0
Net acquisitions	3	5	0	0	0
Reduction in other LT assets	0	0	0	0	0
Addition in other LT liabilities	0	0	0	0	0
Adjustments	0	0	0	0	0
Cashflow after investing acts	**-7**	**-5**	**-5**	**-2**	**20**
Cash dividends	0	0	0	0	0
Equity issue	0	6	0	5	0
Debt issue	0	0	0	0	0
Convertible debt issue					
Others	0	0	0	0	0
Cashflow from financial acts	**0**	**6**	**0**	**5**	**0**
Net cashflow	**-7**	**1**	**-5**	**3**	**20**
Beginning cash	19	12	13	8	11
Ending cash	12	13	8	11	31
Ending net debt	-12	-13	-8	-11	-31

Source: Company data, Nomura estimates

Notes

CUV has performed a capital raising in FY12

Balance sheet (AUDmn)

As at 30 Jun	FY11	FY12	FY13F	FY14F	FY15F
Cash & equivalents	12	13	8	11	31
Marketable securities	0	0	0	0	0
Accounts receivable	1	1	6	12	30
Inventories	0	0	0	0	0
Other current assets	7	2	2	2	2
Total current assets	**20**	**16**	**16**	**25**	**63**
LT investments	0	0	0	0	0
Fixed assets	0	0	0	0	0
Goodwill	0	0	0	0	0
Other intangible assets	0	0	0	0	0
Other LT assets	0	0	0	0	0
Total assets	**20**	**16**	**16**	**25**	**64**
Short-term debt	0	0	0	0	0
Accounts payable	3	2	12	24	63
Other current liabilities	0	0	0	0	0
Total current liabilities	**4**	**2**	**12**	**25**	**63**
Long-term debt	0	0	0	0	0
Convertible debt					
Other LT liabilities	0	0	0	0	0
Total liabilities	**4**	**2**	**12**	**25**	**63**
Minority interest	0	0	0	0	0
Preferred stock	0	0	0	0	0
Common stock	113	119	119	124	124
Retained earnings	-100	-108	-118	-126	-125
Proposed dividends					
Other equity and reserves	3	2	2	2	2
Total shareholders' equity	**16**	**14**	**3**	**1**	**1**
Total equity & liabilities	**20**	**16**	**16**	**25**	**64**
Liquidity (x)					
Current ratio	5.36	6.76	1.26	1.01	1.01
Interest cover	na	na	na	na	na
Leverage					
Net debt/EBITDA (x)	na	na	na	na	na
Net debt/equity (%)	net cash	net cash	net cash	net cash	net cash
Activity (days)					
Days receivable	234.3	501.5	298.0	380.8	353.1
Days inventory	na	na	0.0	0.0	0.0
Days payable	na	na	1,749.5	2,168.5	1,948.4
Cash cycle	na	na	-1,451.4	-1,787.7	-1,595.3

Source: Company data, Nomura estimates

Notes

Cash and marketable securities at the end FY12 was AUD13mn

Positive results from Phase IIa study

CUV announced successful, statistically significant results from its US Phase IIa pilot study (CUV102) of its afamelanotide 16mg implant in the pigmentation disorder Vitiligo. These results show that afamelanotide in combination with narrowband UVB (NB-UVB) therapy significantly improves repigmentation of depigmented lesions in Vitiligo patients compared to NB-UVB as a monotherapy.

The primary study objective was achieved in that extent of repigmentation in the treatment arm was significant (p=0.025/p=0.023, according to two separate quantitative clinical tools that are used to evaluate Vitiligo). From here, CUV will most likely undertake a Phase IIb trial likely to be conducted first in Europe and Asia. This news is in line with our forecasts.

1. Background – what is Vitiligo?

Vitiligo is a common and easily recognized disorder for all dermatologists, many physicians and some observant members of the general public. It is a disorder that is characterized by white spots typically first noted on the fingers, knuckles, around the eyes and mouth, and on the feet. We analysed this market and opportunity in more detail in our 27 March 2012 report entitled, *Opening up the dermatology market*.

The Vitiligo genes activated by environmental agents seem to cause an excessive immune reaction that induces melanocytes to undergo natural cell death and depigmentation of the skin results

There are two basic mechanisms whereby the skin can become white. Melanin is synthesized by melanocyte cells, and is transferred into the surrounding keratinocytes. The keratinocytes transport the melanin from the basal layer of the epidermis to the upper levels. Some disorders inhibit or retard the production of melanin formation and the skin develops lower levels of pigmentation.

Causation of Vitiligo

Vitiligo is acquired destruction of melanocytes. Scientists believe there are three major factors involved in the destruction of melanocytes in patients with Vitiligo:

- **Genetic**: Vitiligo patients inherit a set of three “Vitiligo genes” which predisposes them to destruction of melanocytes;
- **Abnormalities of the melanocyte**: This relates to the melanocytes themselves. Melanocytes from patients with Vitiligo differ from those obtained from a person without Vitiligo; and
- **Susceptibility to activation of melanocytes**: The third factor is susceptibility to an environmental agent that activates (or inhibits) the genes involved, thereby setting in motion the process of destruction of the susceptible melanocytes.

The Vitiligo genes activated by environmental agents seem to cause an excessive immune reaction that induces melanocytes to undergo natural cell death, and depigmentation of the skin results.

Types of Vitiligo

There are two main types of Vitiligo, unilateral (often called “segmental”) and bilateral (usually termed “generalised”):

- **Bilateral, non-segmental or generalised Vitiligo**: this can begin at any age and tends to progress intermittently over the life of the patient. It produces depigmentation that is symmetrical in distribution. This is c80% of all cases of Vitiligo, and is now known as ‘Vitiligo’; and
- **Unilateral (segmental) Vitiligo**: this more commonly begins in children and young adults and progresses for a limited period, usually 1–2 years, and then remains static for the life of the individual. It affects just one side of the body. This is c20% of all cases of Vitiligo.

Clinical history of the disease

Typically, bilateral Vitiligo progresses over the life of the individual, so that the person has partially normal and partially depigmented skin. This probably is the worst outcome. Most people believe it is the worst condition for them to have two colours at least on visible skin such as the hands, face, neck and arms.

What is the current treatment for Vitiligo?

There are a number of treatments for Vitiligo. That said, narrow-band UVB (NB-UVB) phototherapy has emerged as the gold standard of repigmentation treatment in individuals affected by Vitiligo. NB-UVB utilises a localised light source to activate melanin in lesions of the skin. This therapy is known to effectively suppress the local immune response and accelerate the maturity of melanocytes in the area around hair follicles, which act as melanocyte reservoirs. This process leads to activation of melanin. CUV is using afamelanotide as an adjunct to treatment with NB-UVB.

Explanation of the standard treatment – repigmentation in Vitiligo via the hair follicle

Vitiligo recovery depends on a viable melanocyte reservoir, and in many patients with Vitiligo repigmentation is possible when pigment cells are stimulated with appropriate medications. Most stem cell melanocytes originate from the hair follicle unit, where they are present in large numbers and migrate towards the epidermis. A feature of the hair follicle reservoir is the enormous potential for providing pigment cells considering its small size.

The human hair follicle has six main compartments: the connective tissue sheath, the dermal papilla fibroblasts, the outer root sheath, the inner root sheath, the shaft and the sebaceous gland. The mature hair follicle consists of a morphologically permanent upper segment and a lower segment that remodels during hair cycling. In the bulbar region, large differentiated melanocytes located within the hair matrix provide melanin for hair shaft pigmentation. All of these anatomical structures constitute the pigmentary hair follicle unit bearing the melanocyte reservoir.

How does UV light cause stimulation of the bulge?

Ultraviolet radiation produces two effects on Vitiligo skin:

- **Immunosuppression**: UVB may stop melanocyte destruction after UVB irradiation. In this case, T-regulatory (suppressor) cell activity is induced and released after UVB irradiation.
- **Stimulation of growth factors**: cytokines may be activated with UV radiation. Enhanced melanocyte growth factors such as bFGF and ET-1 have been shown after UV radiation. This leads to increased numbers of melanocytes.

Clinically, when vitiliginous lesions (sections of skin which have lost their pigment due to Vitiligo) are repeatedly exposed to an intensive dose of narrowband UVB radiation (308 or 311-313nm), it is common to see small spots, or ‘islands’, of repigmentation forming within the lesion. This occurs because the new melanocytes producing the melanin from the hair follicle bulge have migrated to the skin surrounding the hair follicle. As the melanocytes continue to migrate and produce melanin, these ‘islands’ begin to spread and merge, eventually creating broader, but seldom perfect, repigmentation in the treated area. In this trial, CUV’s afamelanotide + NB-UVB caused increased repigmentation compared to NB-UVB alone.

2. Phase IIa trial results

Primary endpoint reached

The primary endpoint was the extent of repigmentation between Day 0 and Day 168 as measured by the VASI and VETF scores (standard scoring methods for Vitiligo). The extent of repigmentation in the afamelanotide/NB-UVB group was significantly greater than observed in the NB-UVB-alone group (VASI, p=0.025; VETF p=0.023; 95% CI).

What are the VASI and VETF?

- The **Vitiligo Area Scoring Index** (VASI) recording system is a quantitative clinical tool that is used to evaluate Vitiligo and responses to treatment. Basically, the body is divided into five separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. At each follow-up assessment, any macular repigmentation is noted, and the extent of residual depigmentation within each affected patch that had been present at baseline was estimated to the nearest of one of the following percentages: 0, 10%, 25%, 50%, 75%,

90%, or 100%. The total body VASI is calculated by considering the contributions of all body regions.

- The **Vitiligo European Task Force** (VETF) recording system is a quantitative clinical tool that is used to evaluate Vitiligo and responses to treatment. Staging is based on cutaneous and hair pigmentation, and the disease is staged 0–4 on the largest macule in each body region, except hands and feet, which are assessed separately and globally as one unique area. Assessment of spreading is based on Wood's lamp examination of the same largest macule in each body area.

Apart from achieving its primary endpoint, here were a number of other interesting points to note from the trial result:

- **Treatment completion:** Forty-one (75.9%, n=41) patients completed the treatment. Thirteen patients withdrew due to their inability to comply with the demanding treatment protocol, or, in the case of five patients, due to the intensity of pigmentation experienced. Overall the combined treatment was well tolerated and no serious drug-related adverse events were reported;
- **May work better in those with darkest skin (i.e. those most affected by the cosmetic aspects of the disease):** As a subset analysis reflected by the VASI scores, significantly better, more complete and deeper repigmentation was observed for those patients with the darkest skin complexion (phototype IV-VI, n=24) who had received the combination therapy compared to in comparison to those on monotherapy (p=0.046; 95% CI).

What does it mean for CUV?

From here, CUV will most likely undertake a Phase IIb trial likely to be conducted first in Europe and Asia. This news is in line with our forecasts.

Starting from potential approval in 2016F, we believe that if an eventual 10% of US and EU patients were to use afamelanotide, the total CUV NSV opportunity is worth AUD7.62/share. At the current clinical stage, this translates to a risk-weighted NPV of AUD1.63/share from Vitiligo.

3. Other opportunities: CUV application for the treatment of EPP – awaiting a response

CUV believes that increases in skin melanin production through the application of afamelanotide will greatly improve EPP sufferers' total life quality by limiting the skin's light absorption.

EU application – MAA submission

CUV has already announced that final analyses of its confirmatory Phase III European study (CUV029) in erythropoietic protoporphyria (EPP) have shown a clinically relevant, statistically significant prophylactic treatment effect for patients who had been administered its alpha-melanocyte stimulating hormone, afamelanotide (16mg controlled-release formulation).

The primary objective of evaluating afamelanotide in EPP patients was to determine whether the prophylactic effect has meaningful clinical benefit. Afamelanotide treatment aims to allow patients to lead a life which includes exposing themselves to ambient light and to engage in outdoor activities. A similar, secondary objective was to assess the effect of treatment on their Quality of Life (QoL).The key results included:

- Patients receiving afamelanotide reported significantly less pain associated with phototoxicity (median pain score 6.0, p=0.035);
- Patients on active drug experienced half as many phototoxic reactions (p=0.044);
- Afamelanotide enabled patients to experience significantly more direct sunlight exposure without pain (p=0.005); and
- Patients on active drug reported a greater improvement in their Quality of Life (Day 270, p=0.011).

No safety concerns were identified during the study. Due to the results of this study, CUV submitted a Marketing Authorisation Application (MAA) for afamelanotide to the

CUV announced that final analyses of its confirmatory Phase III European study (CUV029) in erythropoietic protoporphyria (EPP) have shown a clinically relevant, statistically significant prophylactic treatment effect for patients who had been administered its alpha-melanocyte stimulating hormone

European Medicines Agency (EMA) in February 2012. Approval would allow CUV to market afamelanotide in all 27 European Union member states as well as Norway, Iceland and Lichtenstein.

To date, four trials in EPP have been completed by the company.

Fig. 1: CUV's EPP clinical trial program

Trial	Phase	Patients enrolled	Study design (months duration)
CUV010	II (EU)	5	Provocation of symptoms by artifical light source (4)
CUV017	III (EU/AU)	101	Cross over study (12)
CUV029	III (EU)	77	2 Parallel arms placebo-active (9)
CUV030	II (US)	74	2 Parallel arms placebo-active (6)
	Total	257	

Source: Company data, Nomura research

Nomura comment

CUV has succeeded in enrolling an impressive number of patients into these trials, considering the rarity of this disease. This may be an indication of the potential patients' willingness to participate, in our view. This is despite the fact that a patient may receive a placebo injection, and hence be subjected to high levels of pain as a part of their disease process. In our view, since high unmet medical need forms a pivotal criterion for the lead regulatory agencies during the evaluation of new therapies, this factor should assist CUV in obtaining approval for afamelanotide.

Submission of CUV's EU registration dossier for afamelanotide occurred on 6 February, 2012. This dossier comprises all manufacturing aspects of the product, chemistry, as well as preclinical and clinical trial data.

The EMA timeline for arriving at a collective decision, and this decision being issued and published by the Committee for Human Medicinal Products (CHMP), normally is between 210 and 360 days after confirmation that a valid application has been received. We believe it is more likely that an orphan drug would receive an opinion at the earlier end of this range.

Valuation methodology and risks

As a result of this news, our risk-weighted valuation for EPP remains at AUD3.38 per share. CUV is already being reimbursed for its product for EPP in select EU countries, and hence the business model has been substantially de-risked, in our view.

Risks to our investment view

We believe that any delay or failure to progress in clinical trials would present downside risk to our target price. That said, faster-than-expected progression to production of CUV's photoprotective technology could provide an upside boost.

Fig. 2: Enter Title Here

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Valuation of CUV R&D portfolio	Risk-weighted valuation (A$ps)	Risk-weighting (in line with Clincial trial stage) (%)	Total opportunity (A$ps)
EPP	$1.75	90%	$1.94
Non-segmental Vitiligo	$1.63	21.4%	$7.62
Valuation	**$3.38**		$9.57

Source: Nomura estimates

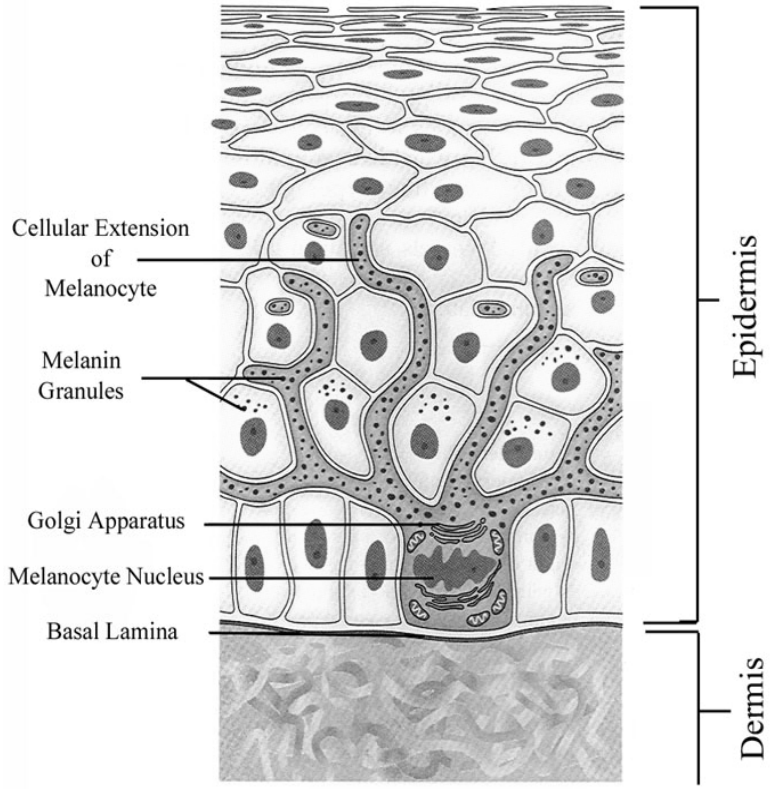
Appendix: Anatomy and afamelanotide

There are a number of different cells in the epidermal (upper) layer of the skin, of which keratinocytes and melanocytes are the most relevant for the purposes of this discussion.

In the skin, the relevant cells include:

- **Melanocytes**: these are cells which produce pigment in the skin and lie at the base of the epidermis, while keratinocytes – both squamous cells and basal cells – make up the majority of the top layer of the skin. Melanocytes live for many years but are significantly less able to multiply. Melanocytes also exist at the root of the hair follicle, in the matrix of the inner root sheath or shaft, and are responsible for giving the hair its colour. Alpha-Melanocyte Stimulating Hormone (α-MSH) molecules cause the production of melanin. To produce melanin naturally, a pathway must be activated by α-MSH binding on the outside surface of the melanocyte. CUV's afamelanotide is a version of alpha-Melanocyte Stimulating Hormone. In the skin α-MSH is expressed by keratinocytes and, less commonly, melanocytes and Langerhans cells, as a protective response to damage caused by ultraviolet radiation;

Fig. 3: Structure of the epidermis of the skin



Source: PubMed

- **Keratinocytes**: these turn over quickly in the skin, migrating from the base to the top of the epidermis as they age and 'sloughing off' at the surface; generally this turnover takes 28 days in healthy adults. The ratio of melanocytes to keratinocytes in healthy skin is 1:36.

What is melanin?

Melanin is a generic term that refers to a group of biopolymers. The chemical composition and physical properties of melanin are dependent on how and where it was formed. Eumelanins and phaeomelanins are the two classes of melanins present in human skin. Eumelanin is the dark brown-to-black pigment and is the form of melanin protective against UV radiation. Phaeomelanin is a red-yellow pigment and is the form of melanin associated most closely with the potential to sunburn easily and to develop skin cancers. Individuals with light coloured skin and brown, blond or red hair tend to have a significant amount of phaeomelanin in their skin, whereas darker-skinned and black-haired individuals have predominantly eumelanin.

α-MSH molecules cause the production of melanin

Melanogenesis and photoprotection

The process whereby melanin is provided in the body is termed melanogenesis. The mechanisms proposed for photoprotection by eumelanin include the absorption and scattering of UV light and quenching of UV light. Melanin in human skin decreases the penetration of UV radiation.

What is alpha-MSH?

The melanocyte-stimulating hormones (MSH) are a class of peptide hormones produced by cells in the intermediate lobe of the pituitary gland in the brain, and other places. Amongst other functions, they stimulate the production and release of melanin (melanogenesis) by pigment cells (melanocytes) in skin and hair. An increase in MSH will generally cause a darkening in humans. However, in people who do not tan well, it is thought that there are variations in their hormone receptors causing them to not respond to MSH in the blood.

Alpha-MSH causes release of melanin

When a person is in the sun or solarium, ultraviolet (UV) radiation penetrates the upper layers of the skin and damages it. This gives the red appearance of sunburn, which signifies increased blood flow to the area in an attempt to repair the damage. It is believed that signals such as fractured DNA particles from the damaged cells are responsible for triggering the release of alpha-MSH from adjacent cells, which migrate to the melanocytes. There is a specific receptor on these cells known as melanocortin receptor-1 (MC1). These receptors are different from the receptors in the central nervous system, known as MC4 and MC5. These cells then produce the tanning molecule, melanin. Melanin production takes several days, and the melanin is formed into small packages which are transferred to the surrounding keratinocytes via the melanocytes' slender processes. These cells, now filled with the dark brown melanin pigment, move towards the surface of the skin and give the skin the 'tanned' look. This is the body's way of protecting the skin from subsequent sunburn. Over several weeks these cells are sloughed off and new cells take their place, causing the tan to fade.

Afamelanotide is an analogue of the peptide hormone alpha-melanocyte-stimulating hormone

What is CUV's afamelanotide?

Developed at the University of Arizona, afamelanotide is an analogue of the peptide hormone alpha-melanocyte-stimulating hormone (alpha-MSH) that tends to induce skin tanning. Natural alpha-MSH has too short a period of usefulness in the body to be practical as a therapeutic drug. Afamelanotide is about 1,000 times more potent than natural alpha-MSH. Afamelanotide stimulates the body's melanocytes (the natural tanning mechanism) to create a tan without needing exposure to damaging levels of UV radiation.

Afamelanotide is administered underneath the skin as an injectable, fully dissolvable implant, about the size of a grain of rice. The implant releases slowly over 10-15 days and slowly releases a supply of afamelanotide into the body. In the current implant, we believe that over 10 days, a total of 16mg of afamelanotide is administered via the subcutaneous implant.

Phase III clinical trials have demonstrated that afamelanotide successfully provides photo-protection against UV-radiation by increasing pigmentation of the skin appearing a few days after administration and lasting up to several months. The results of these trials show that the melanin density change (%) of the subjects who received a single-depot controlled-release formulation was dramatically higher and faster than for the subjects that received a fixed, subcutaneous daily dose for 10 consecutive days, notwithstanding the fact that the former received a substantially lower amount of afamelanotide overall when compared with the latter.

Appendix A-1

Analyst Certification

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Materially mentioned issuers

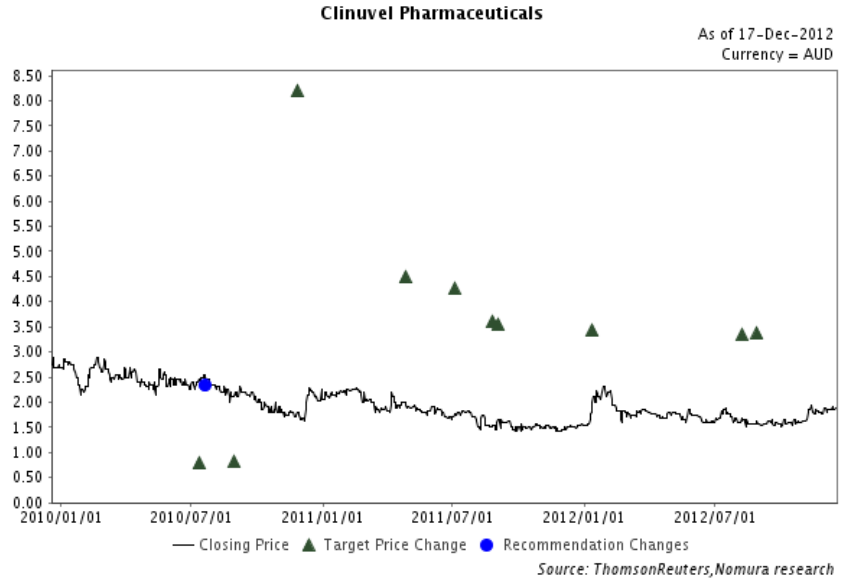
Issuer	Ticker	Price	Price date	Stock rating	Sector rating	Disclosures
Clinuvel Pharmaceuticals	CUV AU	AUD 1.86	18-12-2012	Buy	Not rated	A4,A5

A4 The Nomura Group had an investment banking services client relationship with the issuer during the past 12 months.

A5 The Nomura Group has received compensation for investment banking services from the issuer in the past 12 months.

Clinuvel Pharmaceuticals (CUV AU) **AUD 1.86 (18-12-2012)** Buy (Sector rating: Not rated)

Rating and target price chart (three year history)



Date	Rating	Target price	Closing price
29-Aug-12		3.38	1.63
08-Aug-12		3.34	1.69
12-Jan-12		3.44	1.99
02-Sep-11		3.56	1.65
26-Aug-11		3.62	1.54
04-Jul-11		4.26	1.75
26-Apr-11		4.50	2.00
26-Nov-10		8.20	1.80
30-Aug-10		0.82	2.10
12-Jul-10	Buy		2.45
12-Jul-10		0.80	2.45

For explanation of ratings refer to the stock rating keys located after chart(s)

Valuation Methodology Our risk-weighted valuation for EPP is A$1.75/share. Regarding NSV, starting from potential approval in 2016, We believe that if an eventual maximum of 10% of US and EU patients were to use afamelanotide, the risk-weighted NPV for the NSV opportunity for CUV is A$1.63/share. Our risk-weighted valuation of the CUV pipeline (A$3.38) is our TP.

Risks that may impede the achievement of the target price We believe that any delay or failure to progress in clinical trials would present downside risk to our target price. That said, faster-than-expected progression to production of CUV's photoprotective technology could provide an upside boost.

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STOCKS

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Explanation of Nomura's equity research rating system in Japan and Asia ex-Japan

STOCKS

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