Clinuvel Pharmaceuticals CUV.AX CUV AU

HEALTH CARE & PHARMACEUTICALS

NOMURA
EQUITY RESEARCH

Opening up the dermatology market

Considerable upside should NSV trials be successful

March 27, 2012

Rating Remains	**Buy**
Target price Remains	AUD 3.44
Closing price March 23, 2012	AUD 1.84
Potential upside	+87%

Action: CUV in clinical trials in Non-Segmental Vitiligo (NSV)

NSV is a de-pigmenting disease that affects c10mn persons in the US and EU. CUV's afamelanotide is being evaluated as a combination therapy with narrowband UVB light therapy in two clinical studies in patients with NSV. In early Phase II trial results presented at a recent conference, the NB-UVB plus afamelanotide group showed earlier onset of repigmentation compared to controls.

CUV product would likely the only branded treatment in NSV

We believe the NSV market 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.

Catalyst: CUV upside from potentially successful NSV trials

Starting from potential approval in 2016F, we believe that if an eventual maximum of 10% of US and EU patients were to use afamelanotide, the total CUV NSV opportunity is worth AUD7.73/share. At the current clinical stage, this translates to a risk-weighted NPV of AUD1.65/share from NSV.

Valuation: TP AUD3.44, Buy recommendation

Our risk-weighted valuation for EPP, CUV's other near-term opportunity, is AUD1.78/share. CUV's EU registration dossier for afamelanotide in EPP was submitted on 6/2/12. The EMA should decide whether to approve afamelanotide from 210 to 360 days after complete dossier confirmation.

30 Jun	FY11		FY12F		FY13F		FY14F
Currency (AUD)	Actual	Old	New	Old	New	Old	New
Revenue (mn)	1	2	2	4	4	8	8
Reported net profit (mn)	-11	-11	-11	-9	-9	-7	-7
Normalised net profit (mn)	-11	-11	-11	-9	-9	-7	-7
Normalised EPS	-37.58c	-30.47c	-30.47c	-22.56c	-22.56c	-17.44c	-17.44c
Norm. EPS growth (%)	na	na	na	na	na	na	na
Norm. P/E (x)	na	N/A	na	N/A	na	N/A	na
EV/EBITDA (x)	na	na	na	na	na	na	na
Price/book (x)	3.4	N/A	3.0	N/A	4.7	N/A	8.9
Dividend yield (%)	na	N/A	na	N/A	na	N/A	na
ROE (%)	-53.3	-52.4	-52.4	-45.3	-45.3	-59.4	-59.4
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 an excellent chance of CUV getting afamelanotide to 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.

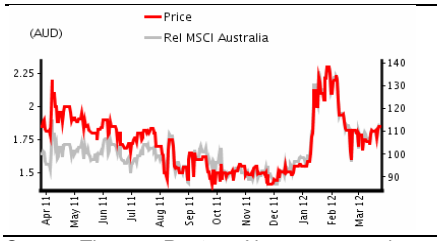
Key data on Clinuvel Pharmaceuticals

Income statement (AUDmn)

Year-end 30 Jun	FY10	FY11	FY12F	FY13F	FY14F
Revenue	**0**	**1**	**2**	**4**	**8**
Cost of goods sold	0	0	-1	-1	-3
Gross profit	**0**	**1**	**1**	**3**	**5**
SG&A	-13	-14	-14	-13	-13
Employee share expense					
Operating profit	**-13**	**-13**	**-12**	**-11**	**-8**
EBITDA	**-13**	**-13**	**-12**	**-11**	**-8**
Depreciation	0	0	0	0	0
Amortisation	-1	0	0	0	0
EBIT	-13	-13	-12	-11	-8
Net interest expense	1	1	1	2	1
Associates & JCEs					
Other income	0	0	0	0	0
Earnings before tax	**-12**	**-11**	**-11**	**-9**	**-7**
Income tax	0	0	0	0	0
Net profit after tax	**-12**	**-11**	**-11**	**-9**	**-7**
Minority interests	0	0	0	0	0
Other items					
Preferred dividends					
Normalised NPAT	**-12**	**-11**	**-11**	**-9**	**-7**
Extraordinary items	0	0	0	0	0
Reported NPAT	**-12**	**-11**	**-11**	**-9**	**-7**
Dividends	0	0	0	0	0
Transfer to reserves	**-12**	**-11**	**-11**	**-9**	**-7**
Valuation and ratio analysis					
FD normalised P/E (x)	na	na	na	na	na
FD normalised P/E at price target (x)	na	na	na	na	na
Reported P/E (x)	na	na	na	na	na
Dividend yield (%)	na	na	na	na	na
Price/cashflow (x)	na	na	na	na	na
Price/book (x)	2.1	3.4	3.0	4.7	8.9
EV/EBITDA (x)	na	na	na	na	na
EV/EBIT (x)	na	na	na	na	na
Gross margin (%)	na	100.0	67.9	67.0	66.0
EBITDA margin (%)	na	-1,205.8	-610.0	-285.1	-108.5
EBIT margin (%)	na	-1,214.6	-614.3	-287.5	-109.7
Net margin (%)	na	-1,096.0	-545.1	-246.0	-95.3
Effective tax rate (%)	na	na	na	na	na
Dividend payout (%)	na	na	na	na	na
Capex to sales (%)	na	6.7	8.6	4.8	2.5
Capex to depreciation (x)	0.6	0.8	2.0	2.0	2.0
ROE (%)	-36.3	-53.3	-52.4	-45.3	-59.4
ROA (pretax %)	-89.1	-139.9	-169.2	-146.1	-81.8
Growth (%)					
Revenue	na	na	93.0	89.4	99.7
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)	-38.00c	-37.58c	-30.47c	-22.56c	-17.44c
Norm EPS (AUD)	-38.00c	-37.58c	-30.47c	-22.56c	-17.44c
Fully diluted norm EPS (AUD)	-38.00c	-37.58c	-30.47c	-22.56c	-17.44c
Book value per share (AUD)	0.87	0.54	0.61	0.38	0.20
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)	-17.6	29.1	-9.0
Absolute (USD)	-17.0	43.1	-3.4
Relative to index	-18.0	21.3	3.1
Market cap (USDmn)	70.3		
Estimated free float (%)	100.0		
52-week range (AUD)	2.31/1.4		
3-mth avg daily turnover (USDmn)	0.03		
Major shareholders (%)			
JM FG	6.9		

Source: Thomson Reuters, Nomura research

Notes

Revenues started for CUV in FY11

Cashflow (AUDmn)

Year-end 30 Jun	FY10	FY11	FY12F	FY13F	FY14F
EBITDA	-13	-13	-12	-11	-8
Change in working capital	8	3	-2	1	2
Other operating cashflow	-7	0	1	1	1
Cashflow from operations	**-12**	**-9**	**-13**	**-9**	**-6**
Capital expenditure	0	0	0	0	0
Free cashflow	**-12**	**-10**	**-13**	**-9**	**-6**
Reduction in investments	0	0	0	0	0
Net acquisitions	10	3	2	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	**-2**	**-7**	**-10**	**-9**	**-6**
Cash dividends	0	0	0	0	0
Equity issue	0	0	20	0	0
Debt issue	0	0	0	0	0
Convertible debt issue					
Others	0	0	0	0	0
Cashflow from financial acts	**0**	**0**	**20**	**0**	**0**
Net cashflow	**-2**	**-7**	**10**	**-9**	**-6**
Beginning cash	22	19	12	22	13
Ending cash	19	12	22	13	7
Ending net debt	-19	-12	-22	-13	-7

Source: Company data, Nomura estimates

Notes

Cash burn should increase in line with progression of clinical trials

Balance sheet (AUDmn)

As at 30 Jun	FY10	FY11	FY12F	FY13F	FY14F
Cash & equivalents	19	12	22	13	7
Marketable securities	0	0	0	0	0
Accounts receivable	0	1	2	4	7
Inventories	0	0	0	0	0
Other current assets	9	7	7	7	7
Total current assets	**29**	**20**	**31**	**23**	**21**
LT investments	0	0	0	0	0
Fixed assets	0	0	-2	-2	-2
Goodwill	0	0	0	0	0
Other intangible assets	0	0	0	0	0
Other LT assets	0	0	0	0	0
Total assets	**30**	**20**	**28**	**21**	**19**
Short-term debt	0	0	0	0	0
Accounts payable	3	3	3	5	10
Other current liabilities	0	0	0	0	0
Total current liabilities	**3**	**4**	**3**	**5**	**11**
Long-term debt	0	0	0	0	0
Convertible debt					
Other LT liabilities	0	0	0	0	0
Total liabilities	**3**	**4**	**3**	**6**	**11**
Minority interest	0	0	0	0	0
Preferred stock	0	0	0	0	0
Common stock	113	113	133	133	133
Retained earnings	-89	-100	-111	-121	-128
Proposed dividends					
Other equity and reserves	2	3	3	3	3
Total shareholders' equity	**26**	**16**	**25**	**16**	**8**
Total equity & liabilities	**30**	**20**	**28**	**21**	**19**
Liquidity (x)					
Current ratio	9.59	5.36	10.08	4.27	1.97
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	na	234.3	259.8	260.8	256.2
Days inventory	na	na	0.0	0.0	0.0
Days payable	na	na	1,753.9	1,155.4	1,103.4
Cash cycle	na	na	-1,494.1	-894.6	-847.3

Source: Company data, Nomura estimates

Notes

FY11 cash and marketable securities were AUD20mn

Expanding the treatment field for skin disorders

CUV continues to progress clinical trials in Vitiligo, as well as getting closer to global approval of its product, afamelanotide, as a treatment for EPP. We continue to believe treatment of Vitiligo with CUV's afamelanotide could provide an elegant solution to what is a disfiguring disease with a large unmet clinical need, whilst larger revenues from EPP treatment should occur in the near-term.

Summary

CUV aims to show that its lead compound, afamelanotide, has efficacy against several sun-related diseases. Afamelanotide is a synthetic analogue of a hormone called alpha-melanocyte-stimulating hormone, or alpha-MSH. This hormone is released when ultraviolet (UV) radiation from the sun penetrates the upper layers of skin and causes damage, stimulating melanin production in the skin.

We have adopted our valuation of the CUV pipeline (i.e. AUD3.44) as our target price

Fig. 1: Photodermatologic diseases

Disorder	Wavelength (nm)	Symptoms	Prevalence
Polymorphous Light eruption	300-600	Subactute rash, itching, generalised erythema. Transient in spring, diminshing in intensity through summer	10-20% of Caucasian Population, 18% of Europeans
Actinic Prurigo (HLA positive)	300-600	Subacute rash, itching, erythema generalised	Unknown, seen in American Indian and Mexican Popn
Chronic Actinic Dermatitis			16.5 per 100,000
Solar Urticaria	350-550	Acute oedematous reaction, anaphylactic reaction to UV light, most prominent in Spring and Summer	3.1 per 100,000
Discoid Lupus Erythematosis	300-650	Chronic and Recurrent light sensitive episodes of LE on exposed body surfaces	27.7 per 100,000
Erthyropoietic Protoporphyria	408-620	Acute phototoxicity after light exposure	1 per 75,000
Congenital Erythropoietic Porphyria	410		1 per 100,000

Wavelength = corresponds to wavelength of light that at which disease is seen
Source: PubMed, Nomura research

EPP

CUV has succeeded in enrolling an impressive number of patients into its EPP 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.

Photodermatology is the subspecialty which focuses on skin disorders which are triggered or aggravated by UV or light of a particular wavelength.

In early Phase II and Phase III trials, afamelanotide has been shown to mitigate or prevent the symptoms in polymorphous light eruption, solar urticaria, and EPP. These photodermatoses vary in onset, character and severity. CUV has focussed its program on thosephotodermatoses which are most severe in nature and for which there is no current therapy, like EPP.

Vitiligo

CUV has previously announced that it is investigating the effectiveness of afamelanotide in Non-Segmental Vitiligo, a condition that affects up to 45mn people globally. This is a new medical indication for afamelanotide. CUV plans to use afamelanotide as an adjunct to the current mainstay of treatment, narrow band UVB (NB-UVB), as well as testing afamelanotide as a single treatment option.

In a large number of clinical trials afamelanotide has been shown to be safe. As well as the potential to increase the response to NB-UVB therapy, afamelanotide has the potential to decrease the theoretical risk of skin damage from currently elevated doses of

UV that are a necessary part of NB-UVB therapy. In addition, we believe positive clinical trial results of afamelanotide should increase the perception of medical necessity.

Afamelanotide is being evaluated as a combination therapy with narrowband UVB light therapy in two clinical studies (CUV101 in Europe and CUV102 in the US) in patients with Non-Segmental Vitiligo (NSV). In early Phase II trial results presented at a scientific conference, the NB-UVB plus afamelanotide group provided earlier onset of follicular and/or diffuse repigmentation compared to controls.

Valuation

Our risk-weighted valuations for the near-term opportunities in the CUV pipeline are shown below.

Fig. 2: CUV – risk weighted valuation of opportunities

Valuation of CUV R&D portfolio	Risk-weighted valuation (A$ps)	Risk-weighting (in line with Clincial trial stage) (%)	Total opportunity (A$ps)
EPP	$1.78	90%	$1.98
Non-segmental Vitiligo	$1.65	21.4%	$7.73
Valuation	**$3.44**		$9.71

Source: Nomura estimates, Tufts data

Given this analysis, we use our valuation of the CUV pipeline (i.e., AUD3.44) as our target price.

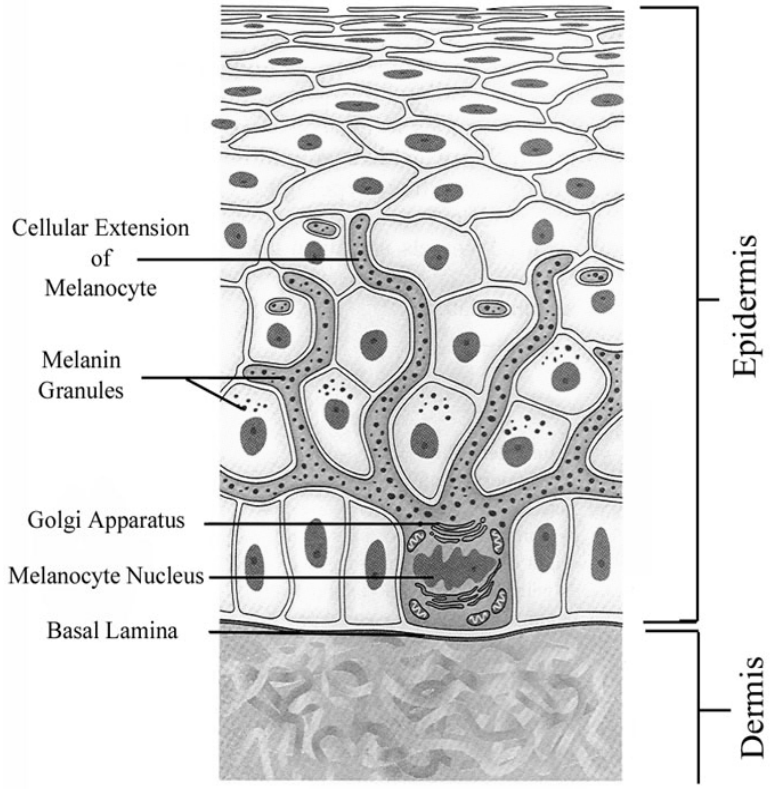
Background – anatomy of the epidermis of the skin

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

α-MSH molecules cause the production of melanin

significant amount of phaeomelanin in their skin, whereas darker-skinned and black-haired individuals have predominantly eumelanin.

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.

What are the effects of light on the skin?

The spectrum of optical radiation (light) is made up of different wavelengths of "light" ranging from 100 nanometers (nm) in the ultraviolet (UV) range to 1 millimeter (mm) in the infrared (IR) range. Visible light spans from about 380nm (violet) to 780nm (red) and

are the "colours" that we see with our eyes. Ultraviolet is invisible and ranges from 380nm down to 100nm, and is further subdivided into UVA, UVB and UVC.

Humans have evolved being exposed to all these wavelengths, so our skin has developed responses to use the light beneficially and to protect us from overexposure (tanning).

Differences in sunlight – UVA and UVB

Ultraviolet (UV) radiation is defined as that portion of the electromagnetic spectrum between x-rays and visible light, i.e., between 40 and 400 nm (30–3 eV). The UV spectrum is divided into:

- Vacuum UV (40-190 nm)
- Far UV (190-220 nm)
- UVC (220-290 nm)
- UVB (290-320), and
- UVA (320-400 nm).

The sun is our primary natural source of UV radiation. Artificial sources include tanning booths, black lights, curing lamps, germicidal lamps, mercury vapor lamps, halogen lights, high-intensity discharge lamps, fluorescent and incandescent sources, and some types of lasers (excimer lasers, nitrogen lasers, and third harmonic Nd:YAG lasers). Unique hazards apply to the different sources depending on the wavelength range of the emitted UV radiation.

UVC is almost never observed in nature because it is absorbed completely in the atmosphere, as are Far UV and Vacuum UV. In humans, UVC is absorbed in the outer dead layers of the epidermis. Accidental overexposure to UVC can cause corneal burns, commonly termed welders' flash, and snow blindness, a severe sunburn to the face. While UVC injury usually clears up in a day or two, it can be extremely painful.

UVB is typically the most destructive form of UV radiation because it has enough energy to cause photochemical damage to cellular DNA, yet not enough to be completely absorbed by the atmosphere. UVB is needed by humans for synthesis of vitamin D; however, harmful effects can include erythema (sunburn), cataracts, and development of skin cancer. Individuals working outdoors are at the greatest risk of UVB effects. Most solar UVB is blocked by ozone in the atmosphere, and there is concern that reductions in atmospheric ozone could increase the prevalence of skin cancer. UVB has higher energy than UVA waves, and UVB waves are therefore more damaging and more carcinogenic. In addition, melanin may have benefits in diseases caused by higher light wavelengths.

Melanin may have benefits in diseases caused by higher light wavelengths

UVA is the most commonly encountered type of UV light. UVA exposure has an initial pigment-darkening effect (tanning) followed by redness (erythema) if the exposure is excessive. Atmospheric ozone absorbs very little of this part of the UV spectrum. UVA is needed by humans for synthesis of vitamin D; however, overexposure to UVA has been associated with toughening of the skin, suppression of the immune system, and cataract formation. UVA light is often called black light. Most phototherapy and tanning booths use UVA lamps.

UVB

The major effects of UVB are that it:

- triggers creation and secretion of new melanin into the skin;
- is thought to cause the formation of moles and some types of skin cancer apart from melanoma;
- causes skin ageing at a slower rate than UVA;
- produces Vitamin D in human skin;
- is more likely to cause a sunburn than UVA as a result of overexposure; and
- is reduced by virtually all sunscreens in accordance with their Sun Protection Factor (SPF).

UVA

The major effects of UVA are that it:

- causes release of pre-existing melanin from the melanocytes;
- causes the melanin to combine with oxygen, which creates the actual tan colour in the skin;
- seems to cause cancer less than UVB, but causes melanoma;
- is blocked less than UVB by many sunscreens but is blocked to some degree by clothing; and
- is present more uniformly throughout the day, and throughout the seasons than UVB.

Narrow-band UVB

NB-UVB is highlighted at 311nm and occurs naturally in sunlight, but not in great amounts.

The action spectrum for "sunburning" of human skin, also known as "erythema", has also been studied. Erythema is dominated by the lower wavelengths (less than 305nm) of the UVB range. Unfortunately, conventional UVB Broadband lamps produce a large amount of "light" in this erythemogenic range. These wavelengths produce burning but have little therapeutic value. What's more, the onset of burning is normally the limiting factor in the amount of UVB that can be administered, and erythema is a major risk factor for skin cancer. Erythema also causes patient discomfort, which may discourage some patients from taking treatments.

More recent studies have confirmed these findings and also determined that UVB Narrowband has fewer burning incidents and longer remission periods than UVB Broadband. When compared to PUVA, UVB Narrowband has significantly fewer side effects and has replaced it in many cases. UVB Narrowband is also capable of producing good therapeutic results without the patient ever reaching the erythemogenic threshold. One disadvantage of UVB Narrowband is that, because the maximum dosage is limited by the onset of slight erythema, and UVB Narrowband is less erythemogenic than UVB Broadband, longer treatment times are required.

Erythropoietic protoporphyria (EPP)

In this section, we explore CUV's near-term opportunity, EPP.

What is EPP?

EPP is a rare and severe genetic disorder causing absolute UV and light intolerance in the skin. Circulating levels of protoporphyrin IX in the skin (due to the genetically determined lack of the enzyme ferrochelatase) cause instant dermal reactions on exposure to light (wavelength >408nm, visible spectrum).

It occurs as a result of an enzyme deficiency that allows for an abnormal build-up of protoporphyrin, a molecule toxic to the body that transforms into excited states on absorption of light energy, causing photo-oxidative damage to the skin. This is manifested through various symptoms such as tingling, stinging, or burning and may accompany the appearance of a rash or blisters. Protoporphyrin build-up also causes general tissue nerve damage that can result in abdomen pain, stomach reflux or, in extreme cases, temporary psychosis. In dealing with the excess protoporphyrin, there is also a high potential for liver damage over time.

The photosensitive effects of EPP can be extremely painful and uncomfortable, often unbearably so. As such, the effect on a patient's lifestyle is normally dramatic. Most patients spend a considerable amount of time and effort avoiding excessive light sources and employing almost complete clothing coverage when possible. Since the photosensitivity results from light in the visual spectrum as well as UV, most sunscreens offer little protection and severe cases may even struggle to find comfort indoors. Ultimately there is no cure for EPP, and limiting light exposure remains the best current treatment option.

EPP is a rare and severe genetic disorder causing absolute UV and light intolerance in the skin

Which doctors treat EPP?

The care of EPP patients is covered by a group of different clinical specialists – haematologists, dermatologists, gastroenterologists and geneticists. Since this rare disease is unknown to general physicians, and since paediatric patients typically incur a 6 to 9 year delay in diagnosis, a number of medical specialists (rather than one) tend to take care of these patients. Hence, in attempting to bring this product to market, CUV have had to educate a larger number of doctor stakeholders than would be seen in other diseases. Indeed, CUV have had the strategy ot connecting directly with patients to treat this disease. This has been primarily been through social media. This has had the effect of expanding word-of-mouth regarding CUV's treatments for both patients and regulatory authorities.

Porphyria patient groups

Patient Porphyria groups tend to be well-defined, as patients have typically organised themselves through patient associations and foundations. These patient associations tend to have linked to different relevant academics and researchers. We believe CUV have strong links with these groups.

Fig. 4: Porphyria patient associations and patient networks

Porphyria patient associations	
EU	Denmark, Finland, France, Germany, Hungary, Italy, Norway, Poland, Spain, Sweden, Switzerland, UK
Americas	Brazil, Columbia, US
ROW	Australia, Japan, New Zealand, South Africa
Porphyria professional networks	
EU	EU Porphyria Initiative, EU Porphyria Network
USA	US Porphyria Research Consortium
Global	Biennial Prophyrins and Porphryria conference

Source: Nomura research

For instance, in each of the EU countries, one central laboratory is appointed to run the specific biochemical diagnostic tests to examine and verify the blood samples taken from each newly suspected Porphyria patient. Centralisation assists the physicians nationwide

to arrive at a standardised and uniform process of diagnosis and counselling. Biochemical tests necessary to confirm any of the nine known variants of Porphyria are validated through the use of a centralised collection and storage of the blood samples in a blood bank.

The advantages of this approach are numerous, including: 1) the long-term ability to access data; 2) follow-up; and 3) pooling of data to advance understanding of this disease.

Current treatment

The systemic medications available for the treatment of systemic exacerbations of the disease are the heme substitutes Normosang (distributed by Orphan Europe) in the EU and Panhematin (distributed by Lundbeck Pharmaceuticals) in the US. However, these treatments do not alleviate the pain from the disease, nor mitigate its course.

CUV application for the treatment of EPP

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).

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

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 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. 5: 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.

US FDA Phase III trial approval

CUV has already received FDA Orphan drug designation (ODD), allowing for an accelerated review process and certain associated privileges.

CUV recently announced that it had reached an in-principle agreement with the US Food and Drug Administration (FDA) to conduct a Phase III study of afamelanotide in EPP. CUV is currently working to finalise its EPP Phase III study (CUV039) protocol with the FDA following an End-of-Phase-II meeting held on March 12, 2012. After the completion of positive pivotal EU EPP studies in 2011 (CUV029 and CUV030), the expectation is that CUV039 will follow a near-identical design. Pending final comments by the FDA, it is expected that this study will start in May 2012.

During previous Phase II and III studies in Europe, the US and Australia, afamelanotide has been shown to enable EPP patients to expose themselves to sunlight without incurring characteristic burns (phototoxicity). As outlined above, in December 2011, CUV announced that final analyses of its Phase III European study (CUV029) in EPP showed a clinically relevant, statistically significant prophylactic treatment effect for patients who had been administered afamelanotide. Hence, we believe there is a high chance of a positive trial of afamelanotide in the US.

Market opportunity

With no real treatment options for EPP sufferers beyond limiting light exposure, Clinuvel's afamelanotide therapy may prove efficacious. The disease is rare, affecting around one in 60,000-200,000 people worldwide, according to PubMed, although accurate statistics are hard to find. We estimate there are between 7,000 and 14,000 EPP sufferers across the US and Europe (c4,000 people in the EU and c6,500 in the US). Afamelanotide appears to be one of the few viable treatment options for EPP.

Recently, CUV announced that it had completed its pre-clinical program for afamelanotide

The highest number of patients is found in the Netherlands, since the disease is originally of Dutch descent. Approximately 20% of patients are children. Through patient organisations and physician associations, patient registries have been formed and maintained over the last decade. In each of the EU countries, as well as in the US, patient registries are known to each of the National or Regional Porphyria Centres.

Italian Law 648/96, Special Access Scheme for EPP – afamelanotide reimbursed

In Italy, due to pressure from physicians and patients, the National Regulatory Agency AIFA included afamelanotide in May 2010 on the list of reimbursable drugs. Under this law, safety data and patients are collected annually. Every two years, a review of clinical benefit is updated.

CUV has negotiated a price of EUR5,375 per injection, given on the basis that patients were eligible for up to six implants annually. On average, we believe Italian patients requested 3.1 implants per year in the first year of eligibility. According to company data, 51 patients received CUV's afamelanotide product, leading to revenues of cUSD1mn.

We believe this significant for a number of reasons. Firstly, it demonstrates that CUV is able to receive reimbursement for a new drug entity. Second, the ongoing nature of this programme demonstrates the requirement for the product on a chronic basis. Third, we believe the EMA is likely to take the Italian programme into account when making its

decision regarding reimbursement on an EU-wide basis. Finally, the ongoing nature of the programme adds to safety data for the treatment.

Should EU and US approval be given, will CUV license the product?
Given the size of the market, we believe CUV will distribute its EPP product itself. To do so, CUV will have to develop expertise to act as a successful distributor. We believe EPP is mainly a disease treated by specialists, mainly in academic and specialised centres and less by primary care physicians. The specific supply of the product may be performed by CUV itself, as it has already supplied the drug for the past six years to these centres.

However, we believe it is possible that CUV will enter into an agreement with a big pharma company to distribute the product. This may be more efficient for CUV, as effective distribution, and penetration of the patient and physician populations may take longer than expected.

CUV enters the Vitiligo market
During the period over the past couple of years that CUV was progressing its EPP opportunity, it has also increased its research into whether afamelanotide was a valid potential option in the treatment of Vitiligo.

Why has CUV moved into Vitiligo?

We believe this is for a number of reasons:

- **Technical**: In developing the EPP opportunity, CUV has gained an understanding of the biological mechanisms of melanogenesis. In addition, the development of expertise in photoprotection led to an understanding of the treatment of other skin diseases such as Vitiligo;
- **Scientific**: During the period that CUV's afamelanotide has been in development, there have been scientific developments in the understanding of melanocytes, in particular that there are melanocyte stem-cells that may be amenable to treatment with CUV's afamelanotide;
- **Commercial**: After the long-term development of afamelanotide and its use in clinical trials, we believe dermatologists are now more comfortable using this new drug, which provides an opportunity for CUV to move into larger markets, and Vitiligo is a larger market opportunity than EPP. In progressing the Vitiligo opportunity, CUV is moving from a company based on prevention of disease (EPP) to more of a company based on the treatment of a disease (Vitiligo).

Vitiligo – afamelanotide potentially expanding the treatment armamentarium for dermatologists

In this section we look at CUV's medium-term opportunity, Vitiligo.

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.

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
- **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. To avoid this, for some patients, the treatment of choice is depigmentation of the normal skin by applications of monobenzone by which they achieve a single colour.

What is the current treatment for Vitiligo?

There are a number of treatments for Vitiligo – the standard treatment is NB-UVB phototherapy. For repigmentation to occur, it is currently thought that it is necessary that stem cell melanocytes in the hair follicle bulge become stimulated with appropriate signals. In this regard, two important properties of melanocytes have to be taken into

consideration: a) neo-melanogenesis, which implies melanin synthesis and production of melanosomes and b) melanocyte migration, which will help pigment cells to reach depigmented skin. This synthesis and migration is mediated by:

- **Cytokines**: A number of these increase melanocyte migration. These can be produced by a number of external influences; and
- **UV light**: Both UVA and NB-UVB are potent melanocyte stimulants for repigmentation; sunlight overexposure with the full UV spectrum may induce marked pigmentation with diffuse skin darkening that depends on the intensity of UV light exposure.

The standard treatment for NSV is NB-UVB phototherapy

Medical therapies

A number of medical therapies, most of which are applied topically, can reduce the appearance of white patches with Vitiligo. These are some of the most commonly used ones:

- **Topical steroid therapy** – Corticosteroid creams may be helpful in re-pigmenting white patches, particularly if they are applied in the initial stages of the disease. Potential side effects include skin shrinkage and skin striae (streaks or lines on the skin).
- **Psoralen photo-chemotherapy** – this is also known as psoralen and ultraviolet A therapy, or PUVA therapy. The goal of PUVA therapy is to repigment the white patches. Psoralen is a drug that contains chemicals that react with ultraviolet light to cause darkening of the skin. The treatment involves taking psoralen orally or applying it to the skin. This is followed by timed exposure to sunlight or to ultraviolet A (UVA) light. There are two major potential side effects of topical PUVA therapy: 1) severe sunburn and blistering and 2) too much repigmentation or darkening (hyperpigmentation) of the treated patches or the normal skin surrounding the Vitiligo. Oral psoralen photo-chemotherapy may also increase the risk of skin cancer, although the risk seems minimal at doses used for Vitiligo.
- **NB-UVB phototherapy** – narrow band UVB (NB-UVB) therapy 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 plans to use afamelanotide as an adjunct to treatment with NB-UVB, as well as testing afamelanotide as a single treatment option. We discuss this in more detail below.
- **Depigmentation** – involves fading the rest of the skin on the body to match the areas that are already white. The major side effect of depigmentation therapy is inflammation (redness and swelling) of the skin.

CUV plans to use afamelanotide as an adjunct to treatment with NB-UVB

Surgical therapies

Surgical therapies are considered only after proper medical therapy is provided:

- **Autologous skin grafts** – This type of skin grafting is sometimes used for patients with small patches of Vitiligo. The doctor removes sections of the normal, pigmented skin (donor sites) and places them on the depigmented areas (recipient sites).
- **Skin grafts using blisters** – In this procedure, the doctor creates blisters on pigmented skin by using heat, suction, or freezing cold. The tops of the blisters are then cut out and transplanted to a depigmented skin area.
- **Micro-pigmentation (tattooing)** – This procedure involves implanting pigment into the skin with a special surgical instrument.
- **Autologous melanocyte transplants** – In this procedure, the doctor takes a sample of normal pigmented skin and places it in a laboratory dish containing a cell-culture solution to grow melanocytes. When the melanocytes in the culture solution have multiplied, the doctor transplants them to depigmented skin patches. This procedure is currently experimental.

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

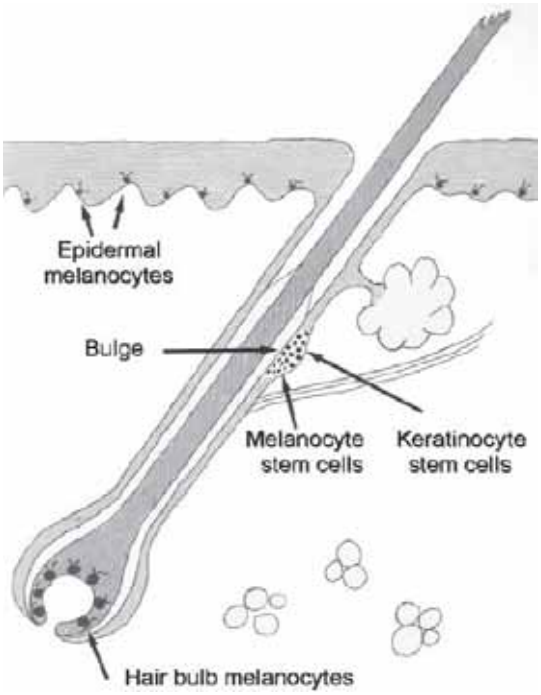
Vitiligo recovery depends on a viable melanocyte reservoir, and in many patients with Vitiligo repigmentation is possible when pigment cells are stimulated with appropriate topical or oral medications. Most stem cell melanocytes originate from the hair follicle unit, where they are present in large numbers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

What is the hair follicle?

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.

Fig. 6: The hair follicle



Source: PubMed

Stem cells within the hair follicle

Mammalian stem cells are divided into two categories:

- **Embryonic**: these are stem cells that may differentiate into all of the specialized embryonic tissues, and
- **Adult**: these are stem cells that are present in adult tissues and are capable of regenerating and maintain the normal tissue turnover and repair by providing new specialized and differentiated cells.

Tissue-specific adult stem cells are usually found in a specialized environment within the hair follicle called the niche or bulge. These cells have the ability for indefinite self-renewal. In this case, after stimulation, some stem cells remain in the niche/bulge and others become a cell that leaves the niche and undergoes cycles of proliferation before transforming into differentiated cells (in this case melanocytes).

The bulge region has been found to be a site of relative immune privilege

These stem cells are located in the lower part of the hair follicle bulge, just below the hair follicle stem cells. The bulge region of the hair follicle, defined as the portion of the outer

root sheath of the hair follicle at the insertion site of the arrector pili muscle, constitutes currently the best characterized site of epidermal stem cell populations.

In addition, the bulge region has been found to be a site of relative immune privilege, protecting the hair follicle epithelial stem cell reservoir from immune attacks, a finding that would constitute a possible explanation for the presence of pigmented hairs in Vitiligo lesions.

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.

Scientific evidence for treatment of Vitiligo with NB-UVB

In a randomized controlled study, Ada et al (2005) concluded that narrowband UVB phototherapy is effective in treating Vitiligo, and the addition of topical calcipotriol does not improve treatment outcome.

Narrow-band UVB phototherapy is effective in treating Vitiligo

In a double-blind randomized study, Yones et al (2007) compared the effectiveness of oral psoralen-UV-A (PUVA) with that of narrowband-UV-B (NB-UVB) phototherapy in patients with NSV. A total of 56 patients received twice-weekly therapy with PUVA or NB-UVB. The change in body surface area affected by Vitiligo and the color match of repigmented skin compared with unaffected skin were assessed after 48 sessions of therapy, at the end of the therapy course, and 12 months after the end of therapy. The results in the 25 patients each in the PUVA and NB-UVB groups who began therapy were analyzed. The median number of treatments was 47 in the PUVA-treated group and 97 in the NB-UVB-treated group ($p = 0.03$); this difference was probably due to differences in effectiveness and adverse effects between the two modalities, such that patients in the NB-UVB group wanted a longer course of treatment. At the end of therapy, 16 (64%) of 25 patients in the NB-UVB group showed greater than 50% improvement in body surface area affected compared with 9 (36%) of 25 patients in the PUVA group. The color match of the repigmented skin was excellent in all patients in the NB-UVB group but in only 11 (44%) of those in the PUVA group ($p < 0.001$). In patients who completed 48 sessions, the improvement in body surface area affected by Vitiligo was greater with NB-UVB therapy than with PUVA therapy ($p = 0.007$). Twelve months after the cessation of therapy, the superiority of NB-UVB tended to be maintained. The authors concluded that in the treatment of NSV, NB-UVB therapy is superior to oral PUVA therapy.

In a randomized, investigator-blinded and half-side comparison study, Casacci and colleagues (2007) compared the effectiveness of NB-UVB phototherapy and 308-nm monochromatic excimer light (MEL) in patients with Vitiligo. A total of 21 subjects with symmetrical Vitiligo lesions were enrolled in this study. Vitiligo lesions on one body side were treated twice-weekly for six months with 308-nm MEL, while NB-UVB phototherapy was used to treat lesions on the opposite side. At the end of the study, six lesions (37.5%) treated with 308-nm MEL and only one lesion (6%) treated with NB-UVB achieved an excellent repigmentation (score 4) while four lesions (25%) treated with 308-nm MEL and five lesions (31 %) treated with NB-UVB showed a good repigmentation (score 3). The authors concluded that it appears that 308-nm MEL is more effective than NB-UVB in treating Vitiligo lesions and it induces repigmentation more rapidly.

Timeline for NB-UVB treatment

The follicular repigmentation with NB-UVB therapy takes time (generally 2-3 weekly treatments for up to 18 months), but is believed to work through two distinct mechanisms within the skin. Firstly, UVB radiation activates the stem cells within the hair follicle bulge to mature and migrate into the epidermis. Secondly, UVB radiation impacts upon keratinocytes within the epidermis, stimulating them to produce α-MSH, which in turn binds to receptors on the melanocyte and activates melanin production.

Unfortunately, this process is not guaranteed to repigment the skin of all patients; approximately 75% of patients see some degree of repigmentation, but the level is not consistent. There is no known time scale involved for repigmentation, nor is there a reliable method to evaluate which patients are suitable for treatment – frustrating factors given the time and financial investment required to undergo NB-UVB therapy. Further, while the wavelengths of light used in NB-UVB are recognised as being less carcinogenic than broadband UVB radiation, and the risks are considered minimal, the long-term effects of this treatment are yet to be fully investigated.

Significant advances in the understanding of the factors which influence melanocytes and their stem cells have led to improved clinical care for patients with Vitiligo. The potential of α-MSH and its analogues to further stimulate these developing melanocytes following ultraviolet therapy, to aid in repigmentation of the vitiliginous skin, is an exciting prospect.

Patient responses to NB-UVB are hugely variable. It is impossible to predict whether Vitiligo will improve as a result of the treatment, and if so, to what extent. Considerable time and resources are required to reach a clinical conclusion as to whether NB-UVB therapy is effective, and there are potential long-term risks associated with repeated exposure to UV radiation, a known carcinogen. Thus, there is a clear argument for the exploration of potential combination therapies with NB-UVB, which could reduce the number of clinical visits required to achieve repigmentation.

Afamelanotide in Vitiligo – should potentiate the response to NB-UVB

How is afamelanotide presumed to treat Vitiligo?

Afamelanotide has a greater binding affinity with the MC1R on melanocytes than natural α-MSH and is therefore able to more readily activate melanin to repigment skin. It is hoped that treatment with afamelanotide, in conjunction with NB-UVB therapy, will produce faster, more consistent repigmentation of vitiliginous skin. Hence, should clinical trials be positive, there is potential for afamelanotide to be a viable option for treatment of the disease, in conjunction with NB-UVB.

Nomura viewpoint: Vitiligo – the next step for afamelanotide

Scientific studies have shown that in Non-Segmental Vitiligo there is a reduction in functional activity of melanocytes. It seems logical that doses of alpha-melanocyte stimulating hormone (afamelanotide) should stimulate underfunctioning melanocytes and should increase the ability of the melanocytes to function under the action of NB-UVB therapy. In our view, the scientific basis for afamelanotide to have a role in the treatment of Vitiligo seems reasonable. The combination therapy of phototherapy and afamelanotide should act to accelerate and deepen the pigmentary response in NSV.

Afamelanotide might stimulate the stem cell melanocytes in the skin, and may help in migration of juvenile melanocytes out of the hair follicle niche and into the skin

In a large number of clinical trials afamelanotide has been shown to be safe. As well as the potential to increase the response to NB-UVB therapy, afamelanotide has the potential to decrease the theoretical risk of skin damage and potential cancer from currently elevated doses of UV that are a necessary part of NB-UVB therapy.

In addition, we believe positive clinical trial results of afamelanotide should increase the perception of the medical necessity of afamelanotide. In turn, we believe this should be noted by regulatory authorities, who have yet to approve afamelanotide.

Potential pharmacoeconomics of afamelanotide in NB-UVB

We have examined the reimbursement profile for narrowband UV therapy. In the US, we believe most, but not all, insurers will reimburse for narrowband UVB. However, the patient is usually responsible for an office visit co-pay. Most light treatments are USD60-

120 per treatment and the patient is expected to pay small (USD20) to moderate (USD50) amounts per visit. Treatments are given 2-3 times per week for as long as 6 months. Hence, we believe the total cost of treatment ranges from USD15,000-75,000 depending on extent of body surface involvement, NU-VB use and whether additional treatments with Excimer laser are required for localized areas of skin involved. We believe some insurers cap the insured patient to a maximum amount of USD40,000 for phototherapy.

In addition, the out-of-pocket expense for a patient may be over USD3,000 per six-month treatment period, and the insurer may have to reimburse over USD9,000 per six-month treatment period.

For instance, the US insurer Aetna considers the following established methods medically necessary for the treatment of Vitiligo:

• Excimer laser;

• Narrow-band ultraviolet B (UVB);

• Topical and oral psoralen photochemotherapy (PUVA); and

• Topical and systemic corticosteroids.

Aetna considers continued PUVA or narrowband UVB therapy not medically necessary unless there is significant follicular pigmentation after 6 months of therapy (8-10 treatments per month).

That said, we believe most EU and US clinicians discontinue treatment if there is no response seen by session 30-38. If no repigmentation islands or peripheral activity is seen, phototherapy is ceased and the patient deemed refractory. We believe this is approximately 10% of population of those with NSV.

What are the potential pharmacoeconomic benefits of afamelanotide?

We believe the number of weeks to assess initial response is 4-8 weeks with a regimen of thrice weekly NB-UVB. We believe that most physicians will deem patients to be non-respondents after 8 weeks of radiation exposure. If patient responds, the treatment can prolonged, ranging from 52-78 weeks to achieve stability.

We believe the average current treatment with Narrow-band UVB costs cUSD34,000. This is shown below.

Fig. 7: Current treatment of Vitiligo

Current treatment of vitiligo with NB-UVB	
Number of weeks to get full response	52
Number of treatments per week	3
Insurance payment per UVB treatment (US$)	120
Physician consultation per UVB treatment (US$)	80
Co-payment per UVB treatment (US$)	20
Total (US$)	34320

Source: Aetna, Nomura estimates

Saving for insurers would be in the order of USD12,000-13,000 per treatment period

We believe the afamelanotide injection (which lasts for 60 days) is likely to be priced at USD1,500 per injection. We believe afamelanotide should act to decrease the time taken for a response to narrowband UVB, and hence be attractive on a pharmacoeconomic basis. If afamelanotide halves narrowband UVB treatment time, then the saving for insurers would be in the order of USD12,000-13,000 per treatment period. This is 37% of the current total cost of treatment of Vitiligo with NB-UVB. In addition, lower exposures to non-ionising radiation could potentially decrease risks of skin cancer in this population.

Fig. 8: Afamelanotide and NB-UVB for the treatment of Vitiligo

Potential new treatment NB-UVB and afamelanotide	
Number of weeks to get full response	26
Number of treatments per week	3
Insurance payment per UVB treatment (US$)	120
Physician consultation per UVB treatment (US$)	80
Co-payment per UVB treatment (US$)	20
Total for UVB (US$)	17160
Injection of afamelanotide (US$)	1500
Number of injections	3
Total for afamelanotide (US$)	4500
Total for use of afamelanotide (US$)	21660
Savings per patient (US$)	12660
Savings a % of total spend on current treatment with UVB	**37**

Source: Aetna, Nomura estimates

Interim results presented

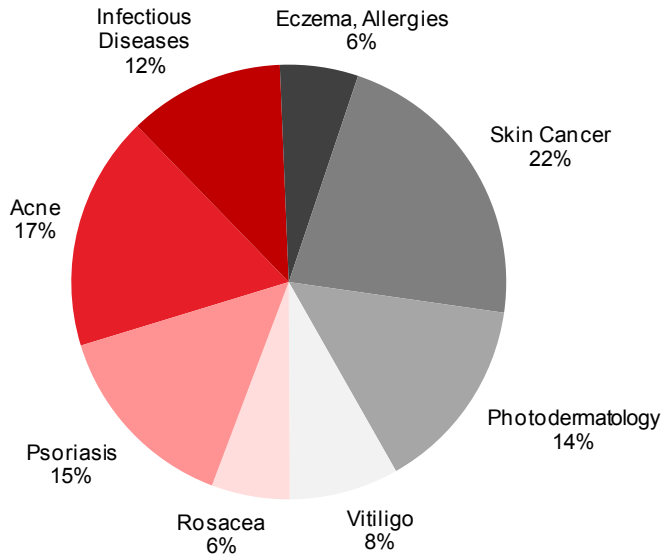
In early Phase II trial results presented at a recent scientific conference, the NB-UVB plus afamelanotide group provided earlier onset of follicular and/or diffuse repigmentation compared to controls.

Afamelanotide has a chance to add to the armamentarium of dermatologists

We believe there are currently eight subsectors of the dermatology treatment market. Indeed, we believe dermatologists tend to subspecialise into these eight sectors. We enclose the current market size of these subsectors below.

Dermatology treatment market is currently worth cUSD17bn pa

Fig. 9: The Dermatology treatment market (current market cUSD17bn pa)



Source: company data, Nomura estimates

The subsectors are explained below:

- **Acne**: We believe acne treatments are dominated by life cycle management and reformulation of active ingredients that have been used for many years. These include antibiotics, retinoids, benzoyl peroxide and combinations of these. The gold standard treatment for severe acne, isoretinoin, was approved in 1982 under the name Accutane, and has been generic since 2002.
- **Psoriasis**: Topical treatments used in this segment include steroids, anthralin, synthetic Vitamin D3 and Vitamin A. The current standard of care is phototherapy, which includes psoralen/UVA, UVB or Laser. In severe patients, itretin, cyclosporine and methotrexate are also given. Finally, there has been the development of monoclonal antibodies to treat these diseases. These include etanercept [Enbrel],

adalimumab [Humira], infliximab [Remicade], and golimumab [Simponi]. These are biologics that block TNF-alpha. In psoriasis and psoriatic arthritis, there is excess production of TNF-alpha in the skin or joints that leads to the rapid growth of skin cells/or damage to the joint tissue. Blocking this leads to a decline in the cycle of disease.

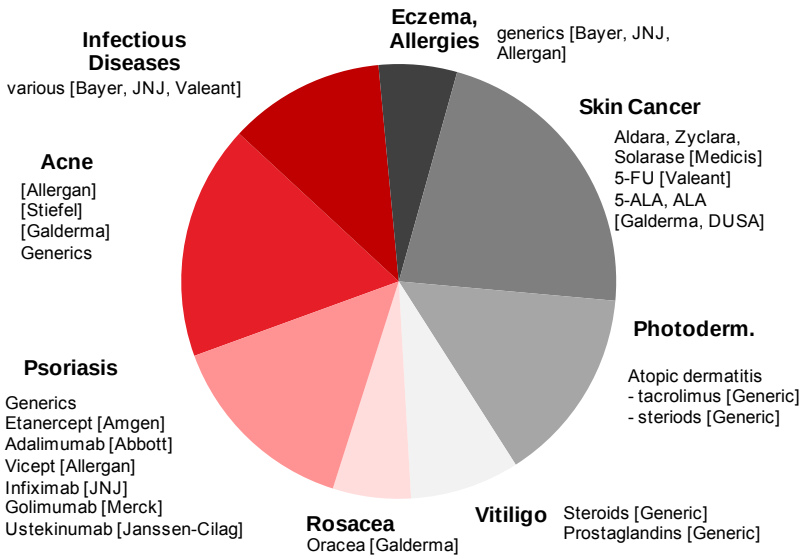
- **Eczema, Allergies**: Emollients and steroid creams are the main therapeutic modalities here;
- **Infectious diseases**: Herpes Simplex and Zoster are the main diseases treated here. Fungal, lice and sexually transmitted diseases also fall in this category;
- **Roseacea**: the major product in this segment is Oracea;
- **Skin Cancer**: in the US, it is estimated that 3.5mn patients received surgical treatment for non-melanoma skin cancer [Skin and Ageing Special Report]. The leading non-surgical therapies in skin cancer are: 1) imiquimod [Aldara] for the treatment for actinic keratosis, HPV-induced warts and BCC; 2) imiquimod [Zyclara] approved in 2010 for the treatment of actinic keratosis of face and scalp; 3) Diclofenac [Solaraze] is used topically to treat superficial BCCs; 4) Photodynamic therapy (PDT) – this is used in premalignant and non-melanoma skin cancer. The EU and ROW markets for PDT are dominated by Metvix, whilst 5-aminolevulinic acid is used in the US. Finally, in January 2012, the FDA approved Picato gel for actinic keratosis.

The established companies in the dermatology market are likely to interested in afamelanotide in Vitiligo, in our view

Should CUV's trials be successful, we believe afamelanotide should expand Vitiligo treatment market as afamelanotide may provide a valid pharmacological solution to a disease that is not very well treated using current treatment methodologies.

We believe the current lack of branded pharmacological treatment in Vitiligo could mean that should afamelanotide be approved as a treatment of Vitiligo, then CUV's afamelanotide product would be of interest to established dermatology players. The established players are shown below.

Fig. 10: Pharmaceutical treatments in the dermatology space



Brackets - companies involved
Source: Company data, PubMed, Nomura research

We believe that, should CUV's trials in Vitiligo be successful, given the nature of the dermatology market, the established players are likely to be interested in some type of alliance with CUV over afamelanotide treatment of Vitiligo. This is because these established players have established salesforces and associated infrastructure that sell to dermatologists, and would be able to add afamelanotide to their sales catalogues.

Should EU and US approval be given, will CUV license the product?
Given the size of the market, we believe CUV will distribute its Vitiligo product via an established pharmaceutical company with an interest in dermatology. We believe it is possible that CUV will enter into an agreement with a big pharma company to distribute the product. This may be more efficient for CUV, as given the size of the potential market, effective distribution, and penetration of the patient and physician populations may take longer than expected.

Profiles of some companies in the dermatology space
Apart from the global pharmaceutical companies that focus on dermatology to a greater or lesser degree, we enclose profiles of selected companies that focus on the dermatology space. These include:

- **Allergan** – Allergan, Inc. (AGN US, unrated) is a multi-specialty health care company focused on discovering, developing and commercializing pharmaceuticals, biologics, medical devices and over-the-counter consumer products. AGN's dermatology portfolio includes tazarotene, a topical receptor selective retinoid approved for psoriasis, as well as Botox (onabotulinumtoxinA) for severe primary axillary hyperhidrosis (excessive underarm sweating) that is not adequately managed by topical agents. 2011 revenues for AGN US were USD5.3bn;
- **DUSA** – DUSA Pharmaceuticals, Inc. (DUSA US , unrated) is a specialty pharmaceutical company focused primarily on the development and marketing of its Levulan photodynamic therapy (PDT) technology platform used in conjunction with its proprietary light source, the BLU-U Blue Light Photodynamic Therapy Illuminator. Levulan Kerastick (aminolevulinic acid) in combination with the BLU-U is approved by the US FDA for the treatment of minimally to moderately thick actinic keratoses (AKs) of the face or scalp. Revenues in 2011 were USD45.2mn;
- **Galderma** – Privately owned Galderma reported sales of EUR1.4bn in 2011, with growth of 11.5% over 2010 at comparable rates. Galderma has c4,000 employees working throughout the world. Galderma's products are distributed in over 70 countries;
- **Medicis** – Medicis Pharmaceutical Corporation (MRX US, unrated) is a specialty pharmaceutical company in the United States focusing primarily on the treatment of dermatological and aesthetic conditions. Since inception in 1988, Medicis has introduced more than 25 new products and formulations. In 2011, Medicis reported revenues of USD721mn; and
- **Valeant** – Valeant Pharmaceuticals International Inc (VRX CN, unrated) is a Canadian pharmaceutical company focused on neurology, infectious diseases and dermatology. Pro forma 2011 Full Year Revenues were C$2.46bn. The company has product sales globally with focus on North America, Central Europe, Mexico, Brazil, and Australia.

Why will doctors like this treatment?
Going forward, in our view CUV will need to balance the shorter time for UVB (the treatment beds are generally owned by the doctor). The doctor is reimbursed per UVB treatment) with increased reimbursement for the doctor from injections of afamelanotide. We will be watching for doctor reimbursement levels from injections of afamelanotide.

Scenario analysis of CUV's Vitiligo opportunity

We have performed a scenario analysis on the potential opportunity for CUV. We believe that if 10% of US and EU patients were to use afamelanotide from FY16F onwards, the total NPV for the NSV opportunity alone for CUV would be AUD7.73/share. This is shown in the following figure.

Fig. 11: Risk-weighted valuation for CUV's NSV opportunity

Valuation of CUV R&D portfolio	Risk-weighted valuation (A$ps)	Risk-weighting (in line with Clincial trial stage) (%)	Total opportunity (A$ps)
Non-segmental Vitiligo	$1.65	21.4%	$7.73

Source: Nomura estimates, PubMed data

We have made a number of assumptions in developing this analysis. These include:

- **Costs to develop this opportunity**: we assume that it will cost CUV AUD50mn to progress this opportunity to end of Phase III clinical trials. This is spent progressively from FY11 to FY16, and is generated from a capital raising by CUV, as well as an upfront payment from a global marketing and distribution partner;
- **Timeline for getting to market**: we assume the Vitiligo opportunity for CUV will get to market in FY16 in the US and EU;
- **Size of the potential market**: we assume CUV will, at least initially, address the US and EU markets for Vitiligo, given their large size and relatively established nature. The numbers of persons with Vitiligo are shown in the following figure.

We assume that in FY16F, CUV will treat 0.1% of the EU and US NSV population

Fig. 12: Number of persons with NSV (EU and US)

(mn)	2012F	2013F	2014F	2015F	2016F	2017F
Northern America	3.1	3.2	3.3	3.4	3.5	3.6
European Union (EU-27)	6.6	6.8	7.1	7.3	7.5	7.7

Source: WHO database, PubMed, Nomura research

The initial target for CUVs afamelanotide is 10% of total NSV patients in the US and EU, and we assume that in FY16F, CUV will treat 0.1% of the EU and US NSV population. Hence, CUV's peak potential penetration is 10%. We assume that the growth in penetration increases at a rate of 50% pa for the first five years, then increases 45% for the next five years.

- **Number of injections**: we assume that three injections are required to treat NSV, given over a six-month period.
- **Reimbursement**: we assume a treatment per injection of USD1,500. As described, this implies a 37% decline in current treatment costs for NB-UVB therapy of Non-Segmental Vitiligo. This price declines 2% per year;
- **Price of the cells per dose**: we assume that the all-in cost of making a dose of afamelanotide is USD300 per dose. This increases 2% per year;
- **COGS for the treatment**: other COGS is 20% of sales, in line with other device companies;
- **CUV's share of EBIT**: we believe CUV will use a distribution partner to market and distribute finished doses of afamelanotide. We assume the net transfer price is calculated after the unit cost of contract manufacturing is factored in. We assume CUV is entitled to 50% of net transfer prices for product sales to its distribution partner;
- **Exchange rate**: we assume exchange rates in line with the Nomura house view. For FY12F, the relevant exchange rates are: 1) AUD/USD - 1.02 and 2) AUD/EUR - 0.76. Our long-term rate for the AUD/USD exchange rate is 0.81;
- **Discount rate**: in line with CUV's WACC, we use a WACC of 15.45% for this scenario analysis. Our assumptions include: 1) Equity beta – due to its inherent risks, CUV will have a higher beta than most other industrial companies. We assume that the company's equity (and asset) beta is 1.70, in line with the average beta for higher-risk biotech opportunities; 2) Nominal long-run growth rate – given the potentially high growth rate of this business, and in line with those of other high-growth companies in the market, we assume a nominal long-run growth rate of 5% and a real long-run growth rate of 2.5%;
- **Probability of success**: according to data from Tufts University, USA, the probability of success of clinical trials depends upon the stage of the clinical trial. We ascribe a 21.4% risk-weighting for the afamelanotide in NSV opportunity, in line with its clinical trial stage.

Fig. 13: Probability of drug at clinical trial stage ultimately getting to market (Tufts DiMasi data)

Phase	Probability of success of moving to next phase (%)	Probability of drug getting on market from particular phase (%)
Phase I	62.5	13.4
Phase II	35	21.4
Phase III	68	61.2
Filing	90	90.0

Source: PubMed, Nomura research

CUV investment case

We enclose our forecasts for the nearest-term potential opportunities for CUV. Our risk-weighted valuations for the near-term valuations in the CUV pipeline are shown below. Given this analysis, we have already adopted our valuation of the CUV pipeline (i.e. AUD3.44 as our target price.

Fig. 14: Valuation methodology

Valuation of CUV R&D portfolio	Risk-weighted valuation (A$ps)	Risk-weighting (in line with Clincial trial stage) (%)	Total opportunity (A$ps)
EPP	$1.78	90%	$1.98
Non-segmental Vitiligo	$1.65	21.4%	$7.73
Valuation	**$3.44**		$9.71

Source: Nomura estimates, Tufts data

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.

Valuation methodology and risks

Our risk-weighted valuation for EPP, CUV's other near-term opportunity, is AUD1.78/share. 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 AUD1.65/share. Given the above analysis, we already adopt risk-weighted valuation of the CUV pipeline as our target price.

Risks to our investment view

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

Appendix A-1

Analyst Certification

I, David Stanton, hereby certify (1) that the views expressed in this Research report accurately reflect my personal views about any or all of the subject securities or issuers referred to in this Research report, (2) no part of my compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this Research report and (3) no part of my compensation is tied to any specific investment banking transactions performed by Nomura Securities International, Inc., Nomura International plc or any other Nomura Group company.

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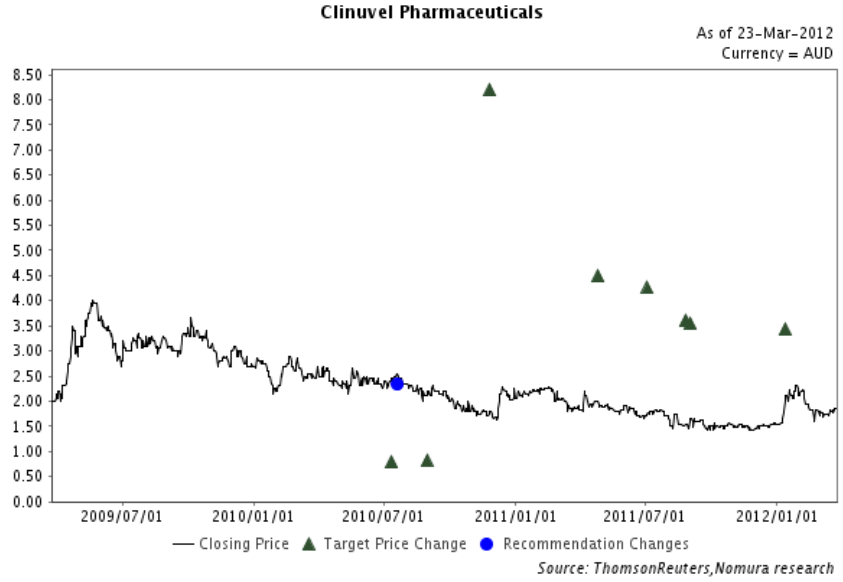
Clinuvel Pharmaceuticals	CUV AU	AUD 1.84	23-Mar-2012	Buy	Not rated	

Previous Rating

Issuer name	Previous Rating	Date of change
Clinuvel Pharmaceuticals	Not Rated	12-Jul-2010

Clinuvel Pharmaceuticals (CUV AU) **AUD 1.84 (23-Mar-2012)** Buy (Sector rating: Not rated)

Rating and target price chart (three year history)



Date	Rating	Target price	Closing price
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$1.78/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$1.65/share. Our risk-weighted valuation of the CUV pipeline (A$3.44) 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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