Cassiopea S.p.A. (SKIN) - 04/07/2015

Cassiopea (SKIN)
Nun ist es also Tatsache, Cassiopea ist gelistet und per Freitag Abend mit rund 400Mio bewertet. Alleine die Griechenlandkrise und der Umstand, dass das Management bestimmt auch lieber zu 34.- anstatt zu 40.- gezeichnet hat war es wohl zu diesem günstigen IPO gekommen. 340Mio Kapitalisierung abzüglich 50Mio Cash bedeutet, dass Cassiopea's Pipeline aktuell mit 290Mio bewertet wird.
Bank Bellevue sagte einen fairen Wert von Cassiopea von 404-442m CHF voraus während Jefferies 485-670m CHF sah.

Fakt ist, das IPO war deutlich überzeichnet. Leider habe ich keine Angabe wieviel genau die Überzeichnung war, aber es dürfte alleine aufgrund der Ausgangslage klar gewesen sein, dass es zu einer regen Nachfrage kommt.
Demnächst werden wohl die Bestände >3% offengelegt werden, geschätzt sieht das wohl aber so aus:
4.9Mio Shares bei Cosmo
1.163 Mio Shares Management & COPN Corner Stone Investors
0.3 Mio Mio Shares Hale & Goostree
3.6 Mio Freefloat

Ich gehe davon aus, dass rund 50% des Freefloat's von Cosmo-Shareholder gekauft wurden, sodass der reale Freefloat wohl nur ca. 1.8Mio Shares beträgt. Die drei IPO-Banken können nochmals 0.363M Shares zuteilen, womit nach meiner Meinung wohl rund 2Mio Shares wirklich handelbar sind was ca. 80Mio Kapitalisierung entspricht. Dadurch dürfte auch klar sein, dass sich die Aktie relativ stark bewegen könnte.

Auch ich frage mich was für eine Kapitalisierung diese Cassiopea verdient hat. Nun, in erster Linie ist das erst einfach mal die Pipeline und somit Hoffnung auf Erfolg dieser Produkte. Wie bewertet man dies?
Mit Winlevi und Breezula besitzt Cassiopea zwei Produkte welche erhebliches Potenzial haben. Hier möchte ich mal ansetzen.

Winlevi Estimates
Jefferies sagt: 350 - 450m$ peak US sales + 125m$ ex-US sales
Bank Bellevue meint: 690m EUR peak US sales + 210m EUR ex-US sales
Credit Suisse meint: 400m$ peak US sales + 100m$ ex-US sales

Wie man sieht schwanken die Vorstellungen sehr stark. Auch die Preisvorstellunge für die Treatments schwanken stark. Klar scheint aber, dass bei Acne das Markt-potenzial in den USA ungefähr so aussieht: 4bn$ pro Jahr zzgl. $1.6bn$ für new novel topical class. Somit dürfte auch die Cassiopea-Vorstellungen von einem 5bn$ Market ungefähr richtig sein für den US-Markt. Wichtig zu wissen ist, dass Acne in US von den Versicherungen bezahlt wird.
Im Acne Markt gibt es kein klares Marktleader-Produkt, daher tun sich die Banken wohl auch schwer sich vorzustellen, dass Winlevi künftig einen höheren Umsatzanteil generieren könnte. Ich bin der Meinung, dass 10-15% vom US-Markt für das erste NCE seit 15 Jahre sowie ca. 50% von diesem Umsatz für Row erzielt werden müsste. Zudem gehe ich davon aus, dass für die US ein Alleingang bevorzugt und für RoW mittels Lizenzdeal gearbeitet wird.

Breezula
Jefferies meint: 135 - 300m$ Peak US sales + 175m$ ex-US sales
Bank Bellevue meint: 260m EUR Peak US sales + 500 bis 600m$ ex-US sales
Credit Suisse meint: 150m$ Peak US sales + 100m$ ex-US sales

Nun, auf Seite 3 habe ich versucht den Produktewert pro Aktie zu berechnen, inkludiert ist ein Diskontierungssatz von 5%. Wenn man die Studiendaten aus Phase2 liest stellt sich also unweigerlich die Frage, wie hoch die Wahrscheinlichkeit von guten Phase3 Resultaten sind. Dahergehend muss man wissen, dass bei Dermatologie die Chancen auf Erfolg deutlich höher stehen als bei anderen Biotechbereichen. Erst Recht, da das Safetyprofil von Winlevi sehr gut aussieht.
Zudem: Winlevi wird in Form einer Crème aufgetragen und nicht wie bei anderen Produkten in Form von Tabletten. Daher ist bei den Studienresultaten auch stetig auf das gute Safety-Profil hingewiesen worden. Die Daten belegen, dass nur bei einigen wenigen Probanden gerine Probleme mit der Haut entstanden sind. Grundsätzlich ist es so, dass krasse Nebenwirkungen wohl bereits in Phase2 aufgetaucht wären, die Chance von positiven Phase3 Resultate dürfte also in der Tat sehr hoch sein.

Inklusive Abdiskontierung komme ich auf Basis 2020-2022 auf eine Wertbasis für Winlevi von 1.75 bis 2.4bn$, was einem Aktienkurs von 175 bis 240 entsprechen würde. Bei vergangenen M&A Transaktionen im Dermabereich wurden in der Regel Umsatz x 3 bis 3.7 bezahlt, auch hier würde dieser Preis also in etwa Sinn machen. Im Falle der Winlevi Peaksales von 7-800m$ x 3 bis 3.7 ergäbe ebenfalls rund 2.1 bis 2.9bn$. Und genau hier denke ich zielt das Cosmo Management auch hin. Durch die Abspaltung der Dermasparte in Cassiopea ist es einfacher, die ganze Firma in Form eines Deals zu verkaufen. Natürlich noch nicht heute, aber wohl irgendwann im Jahr 2017, wenn die Phase3 Results von Winlevi sowie die Phase2 Results von Breezula anstehen. Valeant hat ja ein Right of First Refusal, dies würde mit dem Verkauf umgangen.

Nebenbei erwähnt sei: Im Mai 15 hat man Hale/Goostree 3% von Cassiopea verkauft welche dann die KE mit 1.5Mio gemacht hat und im Gegenzug 297'000 Cassiopea zeichnen konnte. Zuerst lässt das staunen, dass man jemandem zum Preis von 5EUR Shares verkauft, kurz bevor das IPO kommt. Jedoch muss man wissen, dass David Hale (237'000 Shares) ein ausgewiesener Fachmann ist. Er war Chairman von Santarus (bevor sie von 2014 Salix aufgekauft wurde) und Chariman von SkinMedica (bevor sie 2012 von Allergan aufgekauft wurde) und ist aktuell Chairman von Biocept Inc und Conatus Pharmaceuticals welche beide an der Nasdaq kotiert sind. Mit ihm hat man also einen Mann im VR welcher in diesem Bereich über beste Kontakte verfügt und mit seinem Cassiopea-Stake von knapp 3% nun natürlich ein Interesse auf einen Vollerfolg (Takeover) von Cassiopea hat. Frau Goostree (45'000 Shares) hat via Interpid Therapeutics bereits die Winlevi-Phase2 gemacht hat und auch die Phase3 von Winlevi machen wird. Durch diese Transaktion ist es also wohl gelungen, hohes Derma-Knowhow an Cassiopea zu binden welche durch die Shares eine grosse Motivation haben dürfte Winlevi zum Erfolg zu führen. CEO Harbort bekommt für 1Mio$ Shares, womit sie wohl rund 30'000 Shares hält. Ferner gibt es ein ESOP mit 500'000 Shares welche je nach Erfolg verteilt werden. Diese Anreiz Programme und die Möglichkeit nun mittels Shares auch allfällige Produkte oder Derma-Talents einzukaufen gibt dieser Dermasparte so viel mehr Möglichkeiten als wie dies vorher bei Cosmo der Fall gewesen wäre.
Da Cassiopea nun über beste Kontakte im US-Dermamarkt verfügen und diese mittels Aktienprogrammen stark am Erfolg von Cassiopea interessiert sein dürften ist es für mich klar, dass man wohl kaum auf einen Alleingang zielt sondern auf einen Takeover im richtigen Moment schielt. Dank Cosmo als Ankeraktionär können wir zudem sicher sein, dass ein Takeover kaum zu billig über die Bühne gehen würde.

Wenn man davon ausgeht, dass Winlevi zu 60% in Phase3 erfolgreich sein wird, wäre Cassiopea auf Basis 2020 rund 1.05Mrd Wert. Nun, ich bin der Meinung hier muss man noch einen weiteren Risikoabschlag in Betracht ziehen, ich bin der Meinung eine Cassiopea wäre bei ca. 600-650Mio fair bewertet. Jefferies sah Pre-Ipo übrigens einen fairen Wert von 485 bis 670Mio voraus. Nicht vergessen muss man, dass mit Breezula und den anderen beiden Produkten ebenfalls noch ein gewisses Potenzial vorhanden wäre, falls Winlevi versagen würde, alleine Breezula dürfte bis im 2022 im Erfolgsfall rund 750Mio$ Wert haben während das Produkt für Genitalwarzen sowie das zweite Acne-Produkt vom Potenzial her wohl eher im Wertbereich von je 150 bis 300Mio bewegen dürfte.

Overall sehe ich in Cassiopea aber zur Zeit ein Upside-Potenzial von ca. +50% innert 6 Monate als reell gegeben und langfristig dürfte Cassiopea eine sehr interessante Aktie sein welche wohl vom Chancenprofil von -75% bis +750% alles möglich sein kann. Für mich ist das Risikoprofil aufgrund der aktuell doch eher tiefen Kapitalisierung attraktiv, eine Neubeurteilung würde ich bei rund 60 bis 65 CHF in Betracht ziehen. Daher habe ich mich nun auch in Cassiopea positioniert und bin zuversichtlich, dass wir auch mit dieser Aktie aus dem Hause aus Lainate viel Freude haben werden.

Auf Seite 3 stehen die Berechnungen zu Winlevi und Breezula
Auf den Folgeseiten stehen die für mich interessantesten Seiten mit meinen Markierungen aus dem IPO-Prospekt sowie der früheren Studiendaten von Winlevi von 2011.
Disclaimer: Keinerlei Gewähr für Vollständigkeit oder Richtigkeit der Daten und der getroffenen Annahmen.

Cassiopea S.p.A. (SKIN) - 04/07/2015

EUR/USD	1.105
EUR/CHF	1.05
USD/CHF	0.95
Discounted-Factor	5.00%
Shares	10'000'000

Cassiopea Analysis - Winlevi / Breezula

Winlevi & Breezula	2018	2019	2020	2021	2022	2023
Winlevi US $	25.0	120.0	250.0	350.0	450.0	550.0
Manufacturing Costs / SG&A US+Row in %	-80%	-70%	-65%	-60%	-55%	-50%
Manufacturing Costs / SG&A US+Row in $	-20.0	-84.0	-162.5	-210.0	-247.5	-275.0
Winlevi RoW in $	5.0	50.0	100.0	150.0	200.0	250.0
Outlicensed 22%	1.1	11.0	22.0	33.0	44.0	55.0
Income Tax Italy 17% in $	-1.0	-8.0	-18.6	-29.4	-41.9	-56.1
Total Profit Winlevi for Cassiopea	5.1	39.0	90.9	143.6	204.6	273.9
PE	40	30	25	20	17	14
Market Value Winlevi US in $	**202.5**	**1'170.3**	**2'272.1**	**2'871.8**	**3'478.1**	**3'834.6**
Value discounted 5%	**173.6**	**953.2**	**1'758.1**	**2'111.0**	**2'428.9**	**2'544.0**
Value per Share in $	**17.4**	**95.3**	**175.8**	**211.1**	**242.9**	**254.4**
Breezula US $				50.0	100.0	150.0
Manufacturing Costs / SG&A US+Row in %				-80%	-70%	-65%
Manufacturing Costs / SG&A US+Row in $				-40.0	-70.0	-97.5
Breezula RoW in $				50.0	100.0	150.0
Outlicensed 22%				11.0	22.0	33.0
Income Tax Italy 17% in $				-3.6	-8.8	-14.5
Total Profit Breezula for Cassiopea				17.4	43.2	71.0
PE				30	25	20
Market Value Breezula US in $				**522.9**	**1'079.0**	**1'419.3**
Value discounted 5%				**384.4**	**753.5**	**941.6**
Value per Share in $				**38.4**	**75.4**	**94.2**

We intend to focus on product candidates that we believe have expeditious clinical development and regulatory pathways, including product candidates that we believe have demonstrated attractive profiles in early clinical testing and that we can advance into late-stage development, as well as earlier-stage product candidates targeting substantial commercial opportunities that we can quickly and efficiently advance through proof-of-concept studies. We may also seek to in-license and acquire dermatology products that have received regulatory approval for marketing in order to accelerate our entry into the market or expand the portfolio of products we can market to dermatologists.

Market Overview—Acne

Disease description and affected population

Acne, a chronic inflammatory skin disease, is characterized by comedones (blackheads and whiteheads), pimples, and deeper lumps (cysts or nodules) that occur on the face, neck, chest, back, shoulders and upper arms. It is one of the most common reasons for visiting a dermatologist. Globally, it is estimated by Hay *et al* that acne affected 650 million people in 2010. According to the American Academy of Dermatology, 40 to 50 million people within the United States are affected annually, with 85% of all those aged between 12 and 24 getting acne. In 2007 acne represented approximately 25% of the patient volume of dermatologists in the United States, and over 23 million acne prescriptions were written in 2014 in the United States, according to Management's analysis of data from IMS Health, IMS SMART MVP Solutions. See Figure 1 below.

Treatment Mechanics

Acne is believed to result from an interaction of multiple pathogenic or contributing factors ultimately leading to the skin condition. These factors include an overexpression of androgens, an excessive sebum production, a keratinocyte hyperactivity, a follicle occlusion with subsequent infection with the bacterium *Propionibacterium.acnes* and the resulting inflammation. Typically, androgens stimulate the sebaceous glands to produce more sebum than normal; sebum and keratin debris clog the follicle, which is colonized by bacteria. The resulting inflammation leads to the formation of acne. See ''*Product candidate and research program pipeline—Winlevi™*''.

Prescriptions vary according to the degree of acne severity established (American Academy of Dermatology):

- Mild: topical therapy is the standard care for the treatment of mild acne
- Moderate: oral antibiotics are prescribed for moderate and severe acne, and acne that is resistant to topical therapy or that covers a large body surface area; combination therapies using oral antibiotics and topical retinoids have been found to be effective
- Severe: oral isotretinoin is the only medication approved for severe cystic acne, the most serious form of this skin disease

Dermatologists generally prescribe multiple products with complementary mechanisms of action at the same time as the cause of acne is multifactorial:

- seborrhea (excessive sebum production): an anti-androgen, corticosteroid or estrogen is prescribed to inhibit increased sebum production within the sebaceous gland;
- obstruction (clogging of follicles with sebum and keratin): a retinoid is typically used to reduce keratinization within the follicle and the resultant obstruction of the pilosebaceous duct;
- infection with *P. acnes* and inflammation: antibiotics are prescribed to address the infection and reduce inflammation; and
- a product to clean the skin may also be prescribed.

Market Fundamentals and Competition

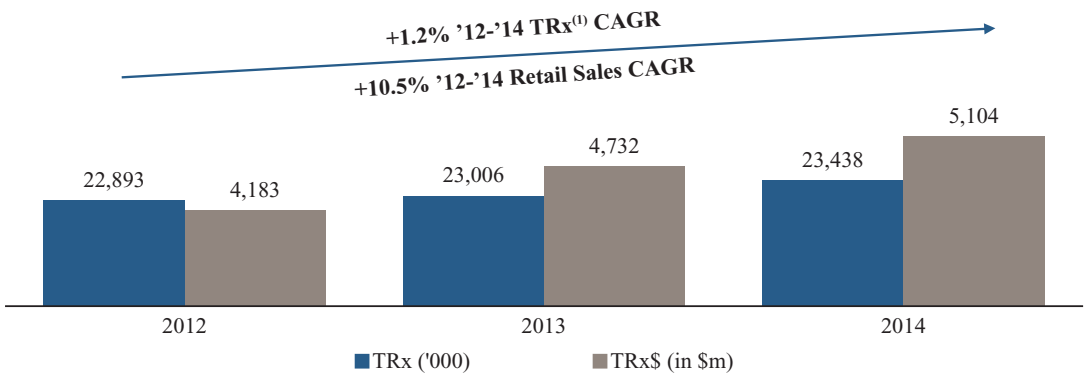
There are currently no topical anti-androgens available on the market targeting androgen to control the complex cascade of events that causes acne. Innovation in the acne market over the last twenty years has been limited, with no NCEs in the United States since the launch of Differin (Galderma) in 1995 and

Tazorac (Allergan) in 1997. Based on Management's analysis of data from IMS Health, IMS SMART MVP Solutions (see Figure 1 for full details) other key products currently in the market include:

- Solodyn (Medicis) launched in 2006—peak U.S. Retail sales of $954 million and 1.3 million prescriptions were achieved in the twelve months to December 2011. Solodyn is an oral antibiotic.
- Epiduo (Galderma) launched in 2008 in Europe and in 2009 in the United States—peak U.S. Retail sales of $392 million and 1.2 million prescriptions were achieved in the twelve months to April 2015. Epiduo is a combination of a topical retinoid and a topical antibiotic.
- Aczone (Allergan) launched in 2008—peak U.S. Retail sales of $345 million and 0.9 million prescriptions were achieved in the twelve months to April 2015. Aczone is a topical anti-infective.
- Benzaclin (Sanofi) launched in 2000—peak U.S. Retail sales of $222 million and 2.0 million prescriptions were achieved in 2006. Benzaclin is a topical antibiotic.
- Acticlate (Aqua Pharmaceuticals, an Almirall company) launched in August 2014—a new version of Monodox, an oral antibiotic. Acticlate achieved U.S. Retail sales of $28 million and 35 thousand prescriptions in the month of April 2015.

According to Management's analysis of data from IMS Health, IMS SMART MVP Solutions, acne accounted for approximately $5.1 billion of Retail sales and 23.4 million prescriptions in the U.S. in 2014, representing a 10.5% CAGR from $4.2 billion and a 1.2% CAGR from 22.9 million prescriptions in 2012, respectively.

Figure 1: U.S. acne market overview



Source: Management analysis of data from IMS Health, IMS SMART MVP Solutions. TRx and Retail sales comprised of:

(i) USC3 Classification 37100 Acne Therapy, Prescription Only, in all specialties.

(ii) Selected anti-acne products Doryx, Monodox, Solodyn and Tazorac, in all specialties.

(iii) TRx and Retail sales within the Dermatology specialty only for Doxycycline HYC DR; Doxycycline Hyclat; Doxycycline Monohyd; Minocycline HCl; Minocycline HCl ER; and Spironolactone.

Reimbursement

In the U.S. market, many prescription medications for the treatment of acne are eligible for reimbursement from the patient's health care insurer. However, as the symptoms of acne are visible, patients can be particularly motivated and willing to pay out of pocket for treatments and higher co-pay associated with Tier 2 and Tier 3 insurance coverage.

Retail prescriptions written by physicians are not always dispensed, as they may be either rejected by payers or abandoned by the patient. According to the IMS Institute for Healthcare Informatics, patients on average abandon approximately 3% of prescriptions and insurers reject approximately 7% of claims. See Figure 2 below. Relative to other classes, acne products have below-average rates of prescription abandonment and payer rejection. We believe that these lower rates further reduce potential future reimbursement risk.

require retreatment. Genital warts can be left untreated; however, they could take a long time to clear up. There are two main types of treatment for genital warts:

- Prescribed topical treatments including, antimitotics (e.g., podophyllotoxin, podophyllin, 5-fluorouracil), caustics (e.g., trichloroacetic acid), interferon inducers (e.g., imiquimod) and sinecatechins (a newer botanical product with an unknown mechanism); and
- Prescribed physical ablation by destroying the tissue of the warts through cryotherapy, electrocautery, excision or laser treatment

Current topical treatments are widely used, however usually require multiple applications typically over a period of four months. Treatment can be ineffective and recurrence is frequent. Furthermore, a number of topical treatments such as Imiquimod are deemed unsafe for use during pregnancy.

Market Fundamentals and Competition

Gardasil, the main drug in the market is only indicated for the prevention of genital warts. The most common approved drugs for the treatment of genital warts are Imiquimod (a generic), Zyclara, Veregen and Condylox.

Product Candidate and Research Program Pipeline

We currently focus on four product candidates in clinical development:

- Winlevi™, for the treatment of acne;
- Breezula™, for the topical treatment of AGA;
- CB-06-02, for the treatment of genital warts; and
- CB-06-01, for the treatment of acne.

Currently, our primary focus is on completing development of Winlevi™, which has completed Phase II. Assuming successful completion of Phase III trials and achievement of regulatory approval, we expect that we would be able to begin commercialization of Winlevi™ in the United States in 2018; we expect that we would be able to begin generating revenue through outlicensing in markets where we do not expect to commercialize the product ourselves promptly after achieving regulatory approval in such markets.

The following table shows certain key information about our product candidates and the related research programs:

Figure 5: Expected timetable

Product	Pre-Clinical	Phase I	Phase II	Phase III	MA / Expected Launch	Next Catalyst	Market Opportunity
Winlevi™ ACNE Anti-androgen **NCE**(1)				H2 2017	2018	H2 2015 (PIII FPI) H1 2017 (PIII LPO)	**US only:** $5bn(2)
Breezula™ ALOPECIA Anti-androgen **NCE**(1)			POC H1 2016 DR H2 2017	H2 2019	2021	H1 2016 (POC)	$1.9bn(3) (surgical) $600m(4) (drugs)
CB-06-01 ACNE Antibiotic **NCE**			POC H1 2016 DR H2 2017	H2 2019	2021	H1 2016 (POC)	**US only:** US$5bn(2)
CB-06-02 HPV Integrin activator **NCE**			POC H1 2016 DR H2 2017	H2 2019	2021	H1 2016 (POC)	**US only:** c.14m new infections (360k reported) each year(5)

POC = Proof of Concept

DR = Dose Ranging

(1) Winlevi™ and Breezula™ are different formulations of the same NCE, for different indications.

(2) Management analysis of IMS Health, IMS SMART MVP Solutions data. Comprised of Retail sales of USC3 Classification 37100 Acne Therapy, Prescription Only, in all specialties, plus Doryx, Monodox, Solodyn and Tazorac in all specialties, plus Doxycycline HYC DR, Doxycycline Hyclat, Doxycycline Monohyd, Minocycline HCl, Minocycline HCl ER, and Spironolactone within the Dermatology specialty only.

(3) International Society of Hair Restoration Surgery. Note: 2012 survey figure.

(4) EvaluatePharma.

(5) Centers for Disease Control and Prevention, January 2014.

Winlevi™

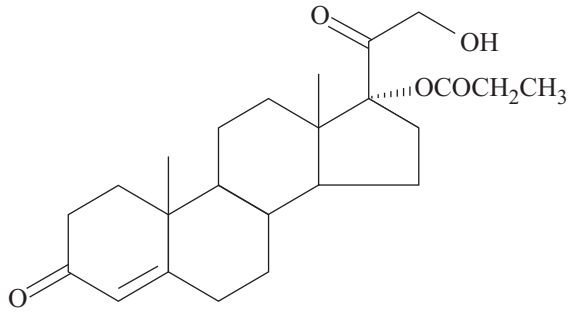
Winlevi™ is the brand name of our anti-androgen for the treatment of acne. It is a topically delivered small molecule that penetrates the skin to reach the androgen receptors of the sebaceous gland. It aims to be the first effective and safe topical anti-androgen that does not have systemic effects. Unlike other hormonal therapies for acne, Winlevi™ can be used by both male and female patients.

Winlevi™ has completed Phase II clinical trials. The FDA is currently evaluating our proposed protocol for Phase III trial.

Product Description

Winlevi™'s active pharmaceutical ingredient, or API, is a steroid belonging to the family of cortexolone derivatives. Chemically, this API is cortexolone 17α-propionate. Its chemical formula is $C_{24}H_{34}O_5$, its molecular weight is 402.5, and its CAS number is 19608-29-8.

Figure 6: Chemical structure of cortexolone 17α-propionate



Winlevi™ is an opaque, white, homogeneous oil-in-water (O/W) emulsion that can be stored at room temperature.

Mechanism of Action

Acne involves a cascade of four physiological events.

- *Seborrhea.* Sebaceous gland cells, or sebocytes, in the skin are androgen-sensitive and contain androgen receptors. When stimulated by androgen hormones, they increase production of sebum, an oily or waxy substance that lubricate and waterproofs the skin and hair.
- *Obstruction.* Excessive sebum and keratin debris obstruct the pilosebaceous follicle, which contains both the sebaceous gland and the root of a hair that grows from the follicle. The obstruction and the continued androgen-stimulated excessive sebum production dilate the follicle, resulting in the formation of the acne lesion, known as a comedo and commonly called a ''blackhead'' or ''whitehead''.
- *Infection.* Bacteria, primarily *P. acnes*, colonize the obstructed follicle.
- *Inflammation.* In presence of bacteria, inflammation occurs and the lesion worsens to papules, which are swollen bumps that contain no visible fluids, and pustules, more severely inflamed swellings that contain fluid. The endpoint of the inflammation process produces nodules and cysts.

Winlevi™ helps to prevent the cascade of events that leads to acne.

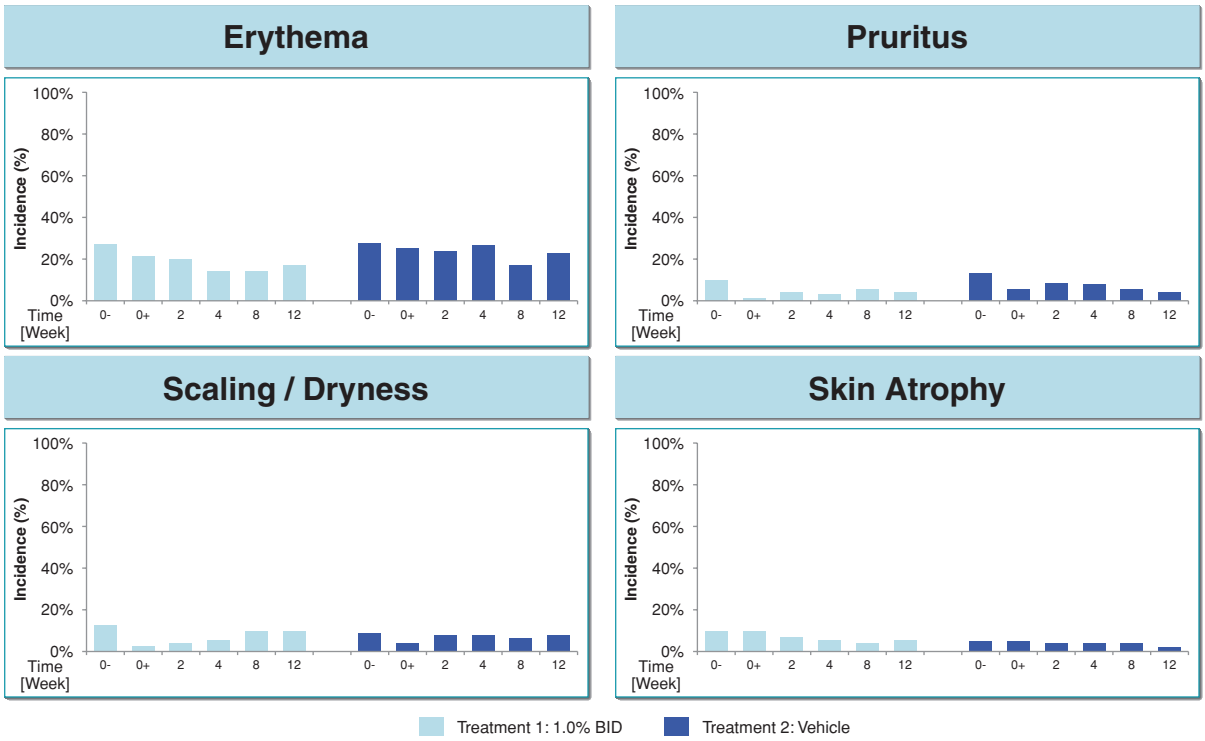
Winlevi™ displaces the androgen hormones from the androgen receptors on the sebaceous gland within the hair follicle. Because the follicle is not obstructed, it does not provide *P. acnes* with the optimal conditions that it needs to colonize the follicle and cause subsequent inflammation.

Winlevi™ is metabolized completely and quickly to cortexolone, a physiological component of the body's endogenous pool of corticosteroids.

Safety

No clinically relevant safety issues were noted with any of the concentrations of Winlevi™ tested and, relative to baseline, no clinically relevant signs of the typical Local Skin Reactions (LSR) generally associated with corticosteroids use were noted. In the HPA / PK study only 3 out of 42 subjects demonstrated a slight abnormality in HPA axis response with modest post-stimulation serum cortisol levels.

Figure 7: LSR equal to placebo in Phase IIb trial



Based on safety to date, and low levels of systemic exposure, FDA granted a waiver for the typically required systemic 2-year carcinogenicity study.

Clinical Trials

To date, Winlevi™ has completed four Phase I studies in a total of 92 subjects, being healthy volunteers and acne patients, and three Phase II studies in 477 subjects with acne. Results of Phase II clinical trials were received in June 2014. The end of Phase II meeting has been achieved in January 2015. The FDA is currently evaluating our proposed protocol for a Phase III trial. The next catalysts for Winlevi™ are First Patient Enrolled, which we expect in the second half of 2015, and Last Patient Out, expected in the first half of 2017.

Highlights of Phase I Program. We conducted four Phase I studies in 92 subjects. 84 of these subjects were healthy while eight patients had acne. The results of these trials showed that Winlevi™:

- was well tolerated;
- showed no measurable serious side effects; and
- permeated the skin and was quantifiable in plasma at very low plasma levels.

Phase II Program. We completed three Phase II trials, two in the United States and one in the European Union, in 2014 with a total of 477 subjects with acne:

- a Phase IIa POC (proof-of-concept) study on 72 patients with acne vulgaris, compared to Retin-A® and placebo;
- a Phase IIb dose-ranging study (DRS) in 363 subjects; and
- an HPA/PK study in 42 subjects.

In the POC study, Winlevi™ has been compared to placebo cream and Retin-A 0.05% as active control, with a treatment of 8 weeks: Winlevi™ resulted statistically superior to placebo in all the endpoints dealing with lesion counts and Acne severity Index, and clinical superior to Retin A cream.

Figure 8: Positive Phase IIa Results

Parameter	Placebo cream (n=14)	Retin-A 0.05% cream (n=30)	Winlevi® 1% cream (n=28)
Total Lesion Count (TLC)			
➢ % reduction vs. baseline, at week 8	37.1	52.5	65.7 (a)
➢ median time (days) to reach improvement 50%	58	57	43 (d)
Inflammatory Lesion Count (ILC)			
➢ % reduction vs. baseline, at week 8	38.9	50.7	67.2 (b)
➢ median time (days) to reach improvement 50%	58	44	36 (e)
Acne Severity Index (ASI)			
➢ % reduction vs. baseline, at week 8	39.5	53.0	68.3 (c)
➢ median time (days) to reach improvement 50%	57	44	42 (f)
Investigator Global Assessment (IGA)			
➢ % of success(g) at week 8	7.1	11.5	22.2

Notes: (a) (p=0.0017 vs. placebo); (b) (p=0.0134 vs. placebo); (c) (p=0.0090 vs. placebo); (d) (p=0.0125 vs. placebo); (e) (p=0.0217 vs. placebo); (f) (p=0.0134 vs. placebo) (g) Success is defined as the proportion of subjects with IGA scores reduction of 2 points with final value no more than 1 at Week 8.

In the Phase IIb (DRS study), aimed to identify the better dose and trial conditions to be proposed for the Phase III studies, Winlevi™ resulted superior to placebo: there was a statistical significant difference in absolute change vs. baseline of total lesions count, inflammatory and non-inflammatory lesions counts among the treatment groups. The 1% BID (twice daily) cohort had a statistically significant decrease ($p<0.05$) compared to placebo in all the lesions counts, including total, inflammatory and non-inflammatory lesions. Furthermore, Winlevi™ 1% BID (twice daily) had a greater proportion of subjects than placebo with at least a 2 points improvement in IGA score, that resulted in a statistically

significant Odds Ratio comparison (2.89), the standard way to compare binary outcomes, i.e. treatment success:

Figure 9: Positive Phase IIb results

Statistical significance in IGA improvement (co-primary endpoint)

ITT	BID 1.0%	VEHICLE	P value
2-Point Improvement	17.1%	6.7%	0.0321

IGA = Investigator Global Assessment.

Statistical significance in total lesion count reduction (co-primary endpoint)

ITT	BID 1.0%	VEHICLE	P value
Mean	(35.7%)	(13.1%)	0.0173

Successful also in secondary endpoint showing reduction in Inflammatory Lesion Counts

ITT	BID 1.0%	VEHICLE	P value
Mean	(37.2%)	(27.0%)	0.0384

Successful also in secondary endpoint showing reduction in Non-Inflammatory Lesion Counts

ITT	BID 1.0%	VEHICLE	P value
Mean	(32.9%)	(16.1%)	0.0178

No clinically relevant safety issues were noted with any of the concentrations of Winlevi™ tested and, relative to baseline, no clinically relevant signs of the typical LSR generally associated with corticosteroids use were appreciated.

In the HPA / PK study only 3 out of 42 subjects demonstrated a slight abnormality in HPA axis response with modest port-stimulation serum cortisol levels.

Phase III Program. Consistent with the results shown in Phase II, our Phase III Program envisages to treat subjects with facial acne with Winlevi™ 1% cream applied twice daily for 12 weeks. In most clinical trials of NCEs for chronic administration, the FDA requires that at least 1,000 patients be treated in order to generate a sufficient safety database. We have submitted a Special Protocol Assessment (SPA) to the FDA, proposing two pivotal trials, each enrolling 700 patients in two arms, treatment and placebo. One trial should be performed in the United States and the other primarily in the European Union, with some additional patients in the United States. The protocols call for subjects of nine years of age and older with moderate to severe acne (Grades 3 and 4 on the IGA score system).

We have interacted with the FDA, in the frame of the SPA discussion. The FDA's, in line with the End of Phase II meeting responses, has recommended certain primary endpoints. The Company fully agrees with the FDA recommendation.

The hierarchical primary endpoints will be the following:

- P1—IGA success at week 12, whereas IGA success is defined as a score of 0 (clear) or 1 (almost clear) and at least a two-point reduction in IGA compared to baseline;
- P2—absolute changes in non-inflammatory lesion counts from baseline to week 12; and
- P3—absolute changes in inflammatory lesion counts from baseline to week 12.

The hierarchical secondary endpoints will be the following:

- S1—Absolute change from baseline in total lesion count at week 12;
- S2—Percent change from baseline in total lesion count at week 12;
- S3—Percent change from baseline in non-inflammatory lesion count at week 12; and
- S4—Percent change from baseline in inflammatory lesion count at week 12.

Because Winlevi™ is a NCE, our Phase III program also includes a long-term, open label safety trial. This trial would expose 300 or more subjects to Winlevi™ for a cumulative six months and a further 100 subjects for a cumulative twelve months by the time of NDA filing (or in time for the 120 day safety update).

We expect to begin enrollment of patients within October 2015 and to have data from the Phase III trials available during at the end of 2017. We have selected Therapeutics Inc. as our CRO provider in the United States and Innopharma S.r.l. as CRO provider in the European Union.

Our IP Rights

Two patent families are protecting Winlevi™ and its API, cortexolone 17α-proprionate, in its polymorphic forms: the first patent family, expiring in United States in 2022/23 and in 2022 in the rest of the world, covers the medical use of the compound for the treatment of acne, alopecia and other diseases; the second patents family covers all the known crystalline forms of the API, the compositions containing the same API and the related medical use in treating acne, AGA and other diseases: this patent family is already issued in United States, Europe, Canada, Japan and other countries, will expire in 2030 in United States and 2028 in the rest of the world.

Breezula™

Breezula™ is the brand name of our anti-androgen-containing composition for the treatment of AGA. Breezula™ is topically delivered to the scalp to reduce the hair miniaturization process that, if not controlled, shrinks the follicle, causing hair thinning and, ultimately, hair loss. Breezula™ is currently undergoing a Phase II proof-of-concept clinical trial in the United States.

Product Description

Breezula™ is a different formulation of the same API contained in Winlevi™. Breezula™ contains a 5% concentration of this API in a lotion designed to penetrate the scalp.

Mechanism of Action

AGA is caused by the overexpression of androgens. These androgens in turn cause excess sebum production that clogs the hair follicles of the scalp, impairing the growth of the hair shaft. The hair becomes thinner and eventually falls out. At the same time, the follicle shrinks progressively and eventually becomes unable to produce new hair.

Breezula™ acts at cutaneous level on the scalp. It antagonizes the negative effects of dihydrotestosterone, the androgen that is the major contributing factor in AGA, on the dermal papillae, small structure in the skin that nourish the hair follicles. Breezula™ also reduces the skin's production of prostaglandin D2, a hormone-like compound that, in elevated levels, can inhibit hair growth. Finally, Breezula™ helps to control sebum secretion, ultimately reducing hair miniaturization and dermal inflammation.

Breezula™ does not interfere with the hormonal and, in particular, androgenic profile of patients; libido and sexual behavior are unaffected in clinical trials to date.

Safety

Because the API of Breezula™ is the same as that of Winlevi™, both product candidates have the same safety profile. Although Breezula™ has a higher concentration of this API, because the scalp is less permeable than facial skin, the systemic penetration of the two product candidates is substantially the same.

Clinical Trials

Breezula™ is currently undergoing a Phase II POC trial in the United States.

Highlights of Phase I Program. We conducted Phase I studies in 18 subjects (16 males and two females) with AGA. A 50mg, 5% solution of Breezula™ was applied to subjects' scalps twice daily for 28 days. The results of these trials showed that:

- Breezula™ penetrates the scalp and appears in the systemic circulation, with approximately 0.25% of the dosage penetrating beyond the skin to reach the circulatory system and only 0.1 to 0.8 nanograms of the metabolite cortexolone detected per milliliter of blood plasma;
- Breezula™ is well tolerated locally (LSR were mild and transient);
- Breezula™ did not cause systemic related side effects; and

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Cortexolone 17α-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study vs. placebo and tretinoin 0·05% cream

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Summary

Background Acne vulgaris is a disorder of the pilosebaceous unit in which the androgens contribute to its onset and persistence. The use of antiandrogens is therefore potentially effective; however, antiandrogens for topical use are not available on the market. Cortexolone 17α-propionate (CB-03-01; Cosmo S.p.A, Lainate, Italy) is a new potent topical antiandrogen potentially useful in acne vulgaris.

Objectives To evaluate the safety and the topical efficacy of CB-03-01 1% cream in acne vulgaris as compared with placebo and with tretinoin 0·05% cream (Retin-A®; Janssen-Cilag).

Methods Seventy-seven men with facial acne scored 2–3 according to Investigator's Global Assessment (IGA) were randomized to receive placebo cream (n = 15), or CB-03-01 1% cream (n = 30), or tretinoin 0·05% cream (n = 32) once a day at bedtime for 8 weeks. Clinical efficacy was evaluated every 2 weeks including total lesion count (TLC), inflammatory lesion count (ILC), acne severity index (ASI) and IGA. Safety assessment included local irritancy score, laboratory tests, physical examination, vital signs and recording of adverse events.

Results CB-03-01 1% cream was very well tolerated, and was significantly better than placebo regarding TLC (P = 0·0017), ILC (P = 0·0134) and ASI (P = 0·0090), and also clinically more effective than comparator. The product also induced a faster attainment of 50% improvement in all the above parameters.

Conclusions This pilot study supports the rationale for the use of topical antiandrogens in the treatment of acne vulgaris. CB-03-01 1% cream seems to fit with the profile of an ideal antiandrogen for topical use.

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Conflicts of interest
L.M. is an employee at Cosmo S.p.A., Lainate (MI), Italy. G.C. is a consultant at Cosmo Research & Development S.p.A., Lainate (MI), Italy.

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Acne vulgaris is a chronic disorder of the pilosebaceous unit in which genetic predisposition, endocrine factors, follicular hyperkeratinization and bacterial infection contribute to its onset and persistence. As sebaceous glands and sebum production are undoubtedly stimulated by the androgen hormones, antiandrogens appear to offer a rational approach to the management of acne vulgaris.[1,2] Nevertheless, the use of antiandrogens could be hampered by the potential occurrence of endocrine side-effects also when applied locally.[3] Thus the profile of an ideal antiandrogen for topical use should include strong activity confined to skin, absence of systemic effects and good tolerability. However, antiandrogens for topical use, endowed with all the above characteristics, are not available on the market.

Cortexolone 17α-propionate (CB-03-01; Cosmo S.p.A, Lainate, Italy) is a new steroidal antiandrogen endowed with strong topical antiandrogenic activity associated with mild anti-inflammatory properties.[4,5] CB-03-01 competes at the human androgen-receptor level[6] without inhibiting the skin 5α-reductase.[7] The steroid easily penetrates human skin[8] and is quickly and extensively metabolized to free inactive cortexolone, thus being devoid of systemic antiandrogenic

effects. The toxicological profile showed that CB-03-01 is well tolerated in rat and rabbit in repeated subcutaneous and dermal toxicities, is not mutagenic, and is not a skin sensitizer.

In adult male volunteers a single skin application of various volumes of CB-03-01 1% cream was very well tolerated with negligible absorption in the bloodstream.[9] All these preclinical and clinical results prompted us to evaluate, in a pilot clinical study, the potential efficacy and the safety of CB-03-01 1% cream in acne vulgaris compared with placebo and with topical tretinoin 0·05% cream (Retin-A®; Janssen-Cilag).

Materials and methods

Study aim and objectives

The study aim was to evaluate the clinical efficacy and tolerability of CB-03-01 1% cream vs. its vehicle alone (placebo) and vs. local tretinoin 0·05% cream in acne vulgaris of mild-to-moderate severity. The primary objective was to demonstrate the clinical and statistical superiority of CB-03-01 1% cream against placebo in improving total lesion count (TLC), inflammatory lesion count (ILC), acne severity index (ASI), and in the proportion of subjects with 'success' outcome at Investigator's Global Assessment (IGA). The secondary objective was to assess the efficacy of CB-03-01 1% cream compared with tretinoin 0·05% cream regarding the same parameters, and evaluating the effect regarding time in days to reach improvement of 50% in TLC, ILC and ASI.

Ethical considerations

The trial was performed in compliance with the ethical principles stated in the Declaration of Helsinki and its subsequent revisions. Study protocol and all other relevant documentation were approved by the Romanian National Authorities and by the relevant local Ethical Committees. The trial was conducted in agreement with Good Clinical Practice and with the applicable European and Romanian regulatory requirements. Prior to participation in the trial, each subject gave his written, informed and witnessed consent.

Participants

Between January and July 2009, three dermatological hospital centres and one outpatient dermatological centre in Bucharest, Romania, screened 83 white-skinned men (age range 18–45 years), 77 of whom were randomized to the treatments. The subjects were affected by acne vulgaris of the face of mild-to-moderate severity, with a score of 2 or 3 on IGA, and with TLC between 20 and 100, and ILC between 10 and 50. Exclusion criteria were: women, presence of facial lesions other than acne vulgaris, use of systemic antiacne medications or any kind of light treatment in the month before starting the study, or topical application of acne medications in the last 2 weeks, history of hypersensitivity to any ingredient of the trial drugs, severe liver or renal impairment, presence of diabetes, glaucoma, psychoses, or severe diseases in other organs including viral or bacterial infections.

Study design and treatment

This pilot clinical study (EudraCT no. 2008-004335-37) was a randomized, double-blind, parallel-group, comparative trial. After completion of screening, the 77 eligible subjects were randomly assigned to three parallel groups. Each group received CB-03-01 1% cream (n = 30), or tretinoin 0·05% cream (n = 32), or placebo (n = 15) constituted by the same excipients of CB-03-01 1% cream (cetyl alcohol, glyceryl monostearate, liquid paraffin, propylene glycol, tocopherol, sodium edetate, polysorbate 80, water). The treatments were thereafter shortly indicated as CB-03-01, tretinoin and placebo, respectively. The products were self-applied in adequate amounts only to the affected areas of the face, once a day at bedtime for 8 weeks. The products were assigned to the subjects in tubes totally indistinguishable according to a blinded randomization list, stratified every six subjects, generated by the sponsor and undisclosed to the investigators and the subjects. Throughout the study duration no additional local or systemic antiacne treatments were allowed, and the subjects were discouraged from starting any new medication without consulting the investigator.

Treatment compliance

Subjects were requested to return, at each visit, all used/non-used medication tubes. The investigator weighed the returned medication tubes, and recorded the returned amounts on drug accountability logs.

Efficacy assessment

The following four variables were assessed at the screening visit and at the end of weeks 2 (visit 1), 4 (visit 2), 6 (visit 3) and 8 (visit 4) of treatment:

TLC and ILC.[10] The count was performed on the right and left sides of the face including the chin, forehead, left and right cheeks. No other regions were considered. TLC included both noninflammatory (comedones) and inflammatory (papules, pustules and nodules) lesions, whereas ILC included only inflammatory lesions. At the screening visit both TLC and ILC values were considered as 100%, and any decrease in the following visits was calculated and regarded as percentage improvement.

ASI.[11] The severity of acne was assessed considering, for each type of lesion, the following correction factors: comedones × 0·5, papules × 1, pustules × 2, and nodules × 3. The total individual severity score was obtained by multiplying the number of each type of lesion with its correction factor, and adding them together. At the screening visit the ASI value obtained was considered as 100%, and any decrease in the

following visits was calculated and regarded as percentage improvement.

IGA.[12] The assessment was made on an ordinal scale with five severity grades, as follows: grade 0, clear skin without inflammatory or noninflammatory lesions; grade 1, almost clear, with rare noninflammatory lesions and no more than one small inflammatory lesion; grade 2, mild severity greater than grade 1, with some noninflammatory lesions and no more than a few inflammatory lesions (papules/pustules only, no nodular lesions); grade 3, moderate severity greater than grade 2, up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion; grade 4, severe, greater than grade 3, up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions. The 'success' outcome at IGA was defined as grade ≤ 1 with a grade 0 or 1 for the subjects whose baseline score was 3, and grade 0 for the subjects with baseline score 2.

Safety assessment

The local tolerability was evaluated at weeks 2, 4, 6 and 8 applying an irritancy score (IS) considering redness, peeling, dryness, swelling, itching and burning, each scored from 0 to 3 according to the severity. Systemic tolerability was evaluated by mean of standard haematology, clinical laboratory, urinalysis, physical examination and vital signs performed at screening and at the end of treatment. Occurrence of adverse events (AEs) was recorded and monitored throughout the study, and during 2 weeks after treatment discontinuation.

Statistical analysis

Data management and statistical analysis were performed by an independent contract research organization (InnoPharma s.r.l., Desio, Italy). The following analysis populations were used: intent to treat (ITT) population, including all randomized subjects who were dispensed study medication with at least one postbaseline assessment, and safety population including all subjects randomized and treated at least once. Main and secondary variables in the comparison between treatments were analysed at a two-sided significance level of $P = 0{\cdot}05$. Treatment differences in the percentage improvement of TLC, ILC and ASI at various weeks, and compared with the screening visit, were assessed by analysis of variance with repeated measures together with a 95% confidence interval (CI). The proportion of subjects with IGA 'success' outcome at various weeks was assessed by the Cochran–Mantel–Haenszel method. The Kaplan–Meier method was used in the survival analysis to analyse the time in days to reach 50% improvement in TLC, ILC and ASI using the two-sided log-rank test. Safety was assessed by the incidence of AEs and by evaluation of vital signs, physical examination, laboratory values and local tolerability. Index of tolerability to the medications was assessed by the same methodology as primary efficacy endpoints or, if the necessary assumptions were not satisfied, in a nonparametric way.

Results

Subject disposition, characteristics and compliance

Subject disposition, characteristics and compliance are reported in Table 1. Eighty-three subjects were screened. Six screen failures occurred, so that 77 subjects were randomized. Of the 77 randomized, 10 subjects did not complete the study as per protocol (four consent withdrawal, six lack of compliance). Seventy-two subjects were analysed both as ITT and safety population (14 in placebo group, 30 in tretinoin group, and 28 in CB-03-01 group). The groups were well balanced regarding demographic characteristics, severity of clinical parameters and proportion of subjects with IGA grade 2 and IGA grade 3. Good and comparable compliance was detected among the groups regarding exposure duration, amount of study drug used, and daily amount of medication self-applied. No concomitant medication potentially interfering with acne outcome or its evaluation was reported.

Efficacy assessment

Total lesion count

The results are reported in Figure 1. Starting from week 2 onwards, the mean reduction of TLC was greater in the CB-03-01 group than in the placebo group, whereas tretinoin showed a profile of activity intermediate between CB-03-01 and placebo groups. The mean ± SD percentage improvement at the final visit was 65·70 ± 31·42 in the CB-03-01 group, 52·51 ± 25·70 in the tretinoin group, and 37·0 ± 33·31 in the placebo group. Considering the improvement at the different visits, CB-03-01 was significantly more active than placebo at weeks 2 (17·9%, 95% CI 0·42–35·37%, $P = 0{\cdot}0447$), 4 (19·9%, 95% CI 2·49–37·44%, $P = 0{\cdot}0254$), 6 (22·4%, 95% CI 4·89–39·85%, $P = 0{\cdot}0124$) and 8 (28·3%, 95% CI 10·75–45·82%, $P = 0{\cdot}0017$). In the comparison with tretinoin, CB-03-01 was always clinically more effective without reaching a statistically significant level. No significant differences, at any time point, were noticed between placebo and tretinoin groups. The time to reach 50% improvement showed significant differences among the groups (log rank test: $P = 0{\cdot}0199$) with a median time of 43·5 days for CB-03-01, 57·0 days for tretinoin, and 58·0 days for placebo (data not shown).

Inflammatory lesion count

The results are reported in Figure 2. Starting from week 2 onwards, the mean ± SD reduction of ILC was greater in the CB-03-01 group than in the placebo and tretinoin groups. The percentage improvement at final visit was 67·26 ± 32·03 in the CB-03-01 group, 50·71 ± 34·46 in the tretinoin group and 38·98 ± 33·22 in the placebo group. Considering the improvement at the different visits, CB-03-01 was significantly more effective than placebo at weeks 4 (22·7%, 95% CI 0·78–44·62%, $P = 0{\cdot}0424$), 6 (22·2%, 95% CI 0·27–44·10%,

Table 1 Disposition, characteristics of subjects and compliance

	Placebo	Tretinoin	CB-03-01
Randomized subjects	15	32	30
Subjects completing the study per protocol	14	26	27
Subjects not completing the study	1	6	3
Consent withdrawal	–	3	1
Lack of compliance	1	3	2
Subjects analysed as ITT population	14	30	28
Subjects analysed as safety population	14	30	28
Age (years), mean ± SD	20·4 ± 1·7	21·2 ± 3·4	20·6 ± 3·5
Weight (kg), mean ± SD	72·9 ± 10·2	77·5 ± 11·9	74·8 ± 9·8
Height (cm), mean ± SD	175·9 ± 7·7	179·5 ± 8·1	178·1 ± 7·5
TLC, mean ± SD	50·6 ± 15·9	48·5 ± 17·2	46·2 ± 15·0
ILC, mean ± SD	33·5 ± 11·4	29·1 ± 10·4	28·5 ± 11·1
ASI, mean ± SD	51·4 ± 19·0	48·2 ± 17·1	45·7 ± 17·4
IGA grade 2, %	57	43	50
IGA grade 3, %	43	57	50
Exposure duration (days), mean ± SD (range)	50·9 ± 3·6 (39–55)	46·8 ± 13·5 (13–55)	51·9 ± 1·8 (46–56)
Total amount of cream used (g), mean ± SD (range)	97·3 ± 48·8 (23·2–203·2)	100·9 ± 65·6 (2·3–221·9)	116·4 ± 65·1 (13·2–221·0)
Daily dose (g), mean ± SD (range)	1·9 ± 0·9 (0·5–3·9)	2·1 ± 1·2 (0·2–4·4)	2·2 ± 1·2 (0·3–4·2)
Concomitant medications	0	0	0

ITT, intent to treat; TLC, total lesion count; ILC, inflammatory lesion count; ASI, acne severity index; IGA, Investigator's Global Assessment.

P = 0·0472) and 8 (27·9%, 95% CI 5·85–49·82%, P = 0·0134). When compared with tretinoin, CB-03-01 was superior at each observation time, and also statistically better at week 6 (19·2%, 95% CI 1·13–37·32%, P = 0·0374). No significant differences, at any time point, were noticed between the placebo and tretinoin groups. The time to reach 50% improvement showed significant differences among the groups (log rank test: P = 0·0490) with a median time of 36·5 days for CB-03-01, 44·0 days for tretinoin and 58·0 days for placebo (data not shown).

Acne severity index

The results are reported in Figure 3. Starting from week 2 onwards, mean ASI improvement was more evident in the CB-03-01 group than in the placebo group. The improvement in the tretinoin group was intermediate between that observed in the CB-03-01 and placebo groups. The mean ± SD percentage improvement at the end of treatment was 68·35 ± 30·58 in the CB-03-01 group, 53·07 ± 33·49 in the tretinoin group and 39·52 ± 31·63 in the placebo group. Considering the

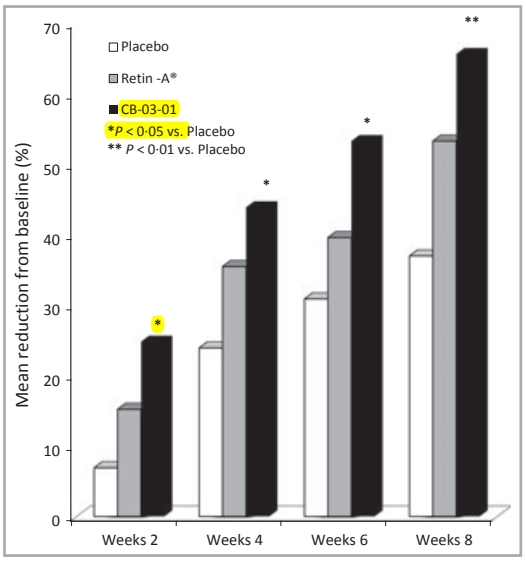

Fig 1. Improvement in total lesion count.

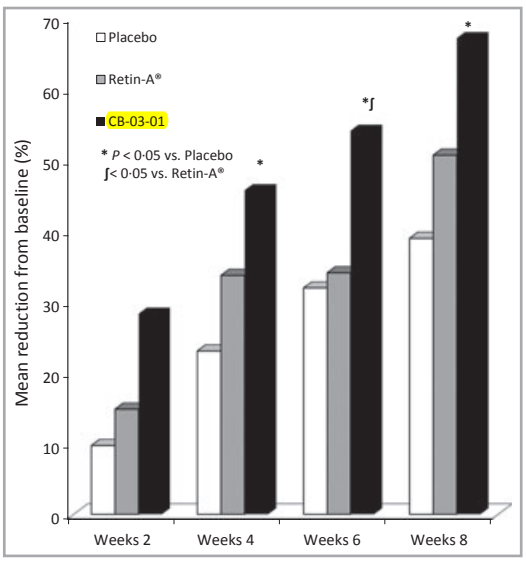

Fig 2. Improvement in inflammatory lesion count.

improvement at the different visits, CB-03-01 was always better than placebo, and this was statistically significant at weeks 2 (22·2%, 95% CI 5·08–39·37%, P = 0·0113), 6 (22·3%, 95% CI 1·19–43·50%, P = 0·0385) and 8 (23·4%, 95% CI 7·17–49·62%, P = 0·0090). When compared with tretinoin, CB-03-01 was clinically but not statistically more effective at each observation time. No significant differences at any time point were noticed between the placebo and tretinoin groups. The time to reach 50% improvement showed significant differences among the groups (log rank test: P = 0·0438) with a median time of 42·5 days for CB-03-01, 44·0 days for tretinoin and 57·0 days for placebo (data not shown).

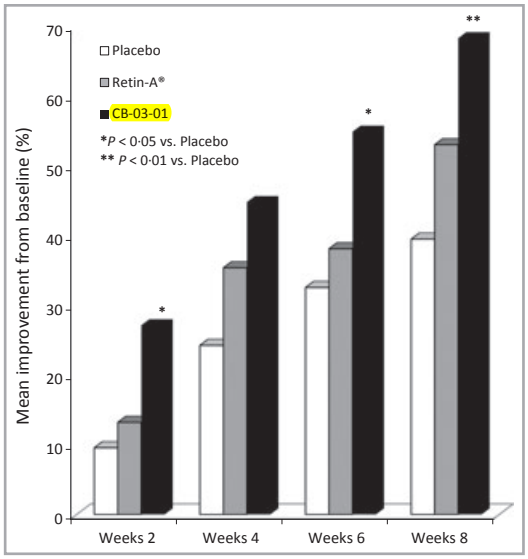

Fig 3. Improvement in acne severity index.

Table 2 Effect on Investigator's Global Assessment

Treatment	Subjects achieving 'success', n (%)	Subjects shifted from score 2–3 to score 0–1, n (%)
Placebo (n = 14)	1 (7)	2 (14)
Tretinoin (n = 26)	3 (12)	7 (27)
CB-03-01 (n = 27)	6 (22)	11 (41)

Investigator's Global Assessment

The results are reported in Table 2. The statistical analysis applied to IGA 'success' did not show significant differences among the treatments. Nevertheless, in the CB-03-01 group a higher proportion of 'success' was detected (22%) as compared with the tretinoin (12%) and placebo (7%) groups. In agreement with these findings, the proportion of subjects reducing to IGA grade between 0 and 1 was notably higher in the CB-03-01 group (41%) than in the tretinoin (27%) and placebo (14%) groups.

Safety assessment

The local tolerability of CB-03-01 was good. In contrast, in the groups treated with tretinoin and placebo an evident worsening of IS was observed within the first 2 weeks. This effect gradually abated to near normal value (≤ 1) at the end of the treatment period (Table 3). An exploratory analysis showed a statistically significant difference between the CB-03-01 and placebo groups at visit 1 (P = 0·0412). Regarding systemic tolerability, no clinically important abnormalities were detected in any treated group in haematology, clinical laboratory, urinalysis, vital signs and other observations related to safety. A total of eight subjects (11%) experienced 14 AEs which were distributed as follows: five in the placebo group, six in the tretinoin group, and three in the CB-03-01 group (Table 4). The most frequently reported AEs were laryngitis, herpes simplex, pruritus and acne worsening. All AEs were mild or moderate, and none was judged as either serious or requiring withdrawal from the study or treatment discontinuation.

Table 3 Irritancy score improvement

Treatment	Visit 1 (2 weeks)	Visit 2 (4 weeks)	Visit 3 (6 weeks)	Visit 4 (8 weeks)
Placebo				
n	14	14	14	14
Mean ± SD	2·14 ± 2·18	2·14 ± 3·92	1·79 ± 4·46	0·86 ± 2·14
Range	0–8	0–15	0–17	0–8
Tretinoin				
n	30	26	26	26
Mean ± SD	2·20 ± 3·17	1·04 ± 2·13	0·73 ± 1·43	0·62 ± 1·20
Range	0–13	0–10	0–6	0–5
P-value vs. placebo	0·3809	0·2834	0·5257	0·8261
CB-03-01				
n	28	28	28	27
Mean ± SD	1·29 ± 2·42	0·75 ± 1·48	0·57 ± 1·03	0·30 ± 0·61
Range	0–11	0–6	0–3	0–2
P-value vs. placebo	0·0412	0·1015	0·2772	0·6046

Table 4 Adverse events (AEs) by system organ class

AEs	Placebo (n = 14)		Tretinoin (n = 30)		CB-03-01 (n = 28)	
	Events, n	Patients with AEs, n (%)	Events, n	Patients with AEs, n (%)	Events, n	Patients with AEs, n (%)
AEs and patients with any AEs	5	3 (21)	6	2 (7)	3	3 (11)
AEs by system organ class						
Infection and infestations	2	2 (14)	1	1 (3)	1	1 (4)
Metabolism and nutrition disorders	0	0	1	1 (3)	0	0
Musculoskeletal and connective tissue disorders	0	0	1	1 (3)	0	0
Skin and subcutaneous tissue disorders	3	3 (21)	3	2 (7)	2	2 (7)

Discussion

CB-03-01 is a new potent steroidal antiandrogen, with additional anti-inflammatory properties, which was demonstrated in animal models to act selectively at the skin level without systemic effects.[4,5]

The present study was a pilot, randomized, double-blind, comparative trial evaluating the efficacy and the tolerability of CB-03-01 1% cream in acne vulgaris of mild-to-moderate severity, compared with placebo and topical tretinoin. As this trial was the first experience of repeated administration of CB-03-01 to humans, it was deemed prudent to enrol only a limited number of adult males, and not to expose them for too long a period of treatment exceeding 8 weeks. Considering the concerns raised from some Ethical Committees about the need to treat patients only with placebo, the size of the placebo group was reduced.

CB-03-01 was significantly more effective than placebo in improving TLC, ILC and ASI. Worthy of interest is the effect particularly evident on the inflammatory lesions, probably due to the ancillary anti-inflammatory activity of the molecule. All the above effects had already become evident after 2–4 weeks of treatment and increased proportionally thereafter. The faster effect of CB-03-01, as compared with that of placebo and tretinoin, has been also confirmed by the survival analyses showing an evident reduction of number of days required to reach 50% improvement in all parameters. Also in the comparison with tretinoin, CB-03-01 was globally more effective in all above parameters. This finding is of particular interest as topical retinoids have a well-established clinical efficacy in the treatment of acne vulgaris.[13] In our study the clinical activity of tretinoin was very similar to that described in other clinical trials[14–16] but, surprisingly, it was found not significantly better than placebo. This inconsistency could be attributed to the small and unbalanced groups of patients, thus preventing detection of statistically significant differences between tretinoin and placebo despite evident differences of activity. The study did not show statistically significant differences among treatments regarding the 'success' achievement in the IGA at the end of the treatment. Nevertheless, CB-03-01 induced a higher proportion of IGA 'success' than placebo and tretinoin, and also induced a notably higher proportion of subjects in whom the IGA grade 2–3 at screening was reduced to grade 0–1 at the end of the treatment period.

During the study, no concerns were raised regarding the local and systemic safety of CB-03-01. Worthy of interest is the better tolerability of CB-03-01 as compared with tretinoin, already evident at visit 1. This is of practical importance considering that one of the main concerns in using topical retinoids is the appearance of skin irritation in the first weeks of treatment, frequently leading to discontinuation or reduction of the number of applications. No serious AEs were detected through the study, no drop-outs occurred for safety reasons, and no differences among the groups were noticed concerning the nature and the incidence of AEs.

In conclusion, the data provided by this pilot study support the rationale for the use of topical antiandrogens in the treatment of acne vulgaris of mild-to-moderate severity. CB-03-01 was found to be significantly more effective than placebo, clinically better than tretinoin, very quick in onset of clinical effect, and mostly well tolerated.

Considering the preliminary nature of this trial, additional studies including more patients and more international study centres are needed to evaluate the potential of CB-03-01 1% cream in the treatment of acne vulgaris.

What's already known about this topic?

- Antiandrogens are considered potentially effective in treatment of acne vulgaris; nevertheless, antiandrogens for topical use are not yet on the market.

What does this study add?

- This study demonstrated, for the first time, that the topical antiandrogen cortexolone 17α-propionate 1% cream is safe and effective in the treatment of acne vulgaris, as compared with vehicle and topical tretinoin. These data contribute to support the use of topical antiandrogens in the treatment of acne vulgaris.

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