Leading the development
& commercialization
of marine-derived oncology drugs

Pharma Mar

Plitidepsin: Repurposing of a Drug for the Treatment of SARS CoV 2

Interreg Atlantic Area
European Regional Development Fund

EUROPEAN UNION

Blue Human

Fármacos de Origen Marino Desarrollados contra Enfermedades Infecciosas y Oncológicas
BlueHuman Project, 5-Nov-2021

Overview

Leader in development & commercialization of marine derived oncology drugs

Global Fully Integrated Commercial Stage Biotech

Developing marine-inspired oncology drugs

Revenue Generating & Profitable

FY 2020
Rev. €270m | EBIT €156m

3 Approved Oncology Products

Yondelis®
Aplidin®
Zepzelca®

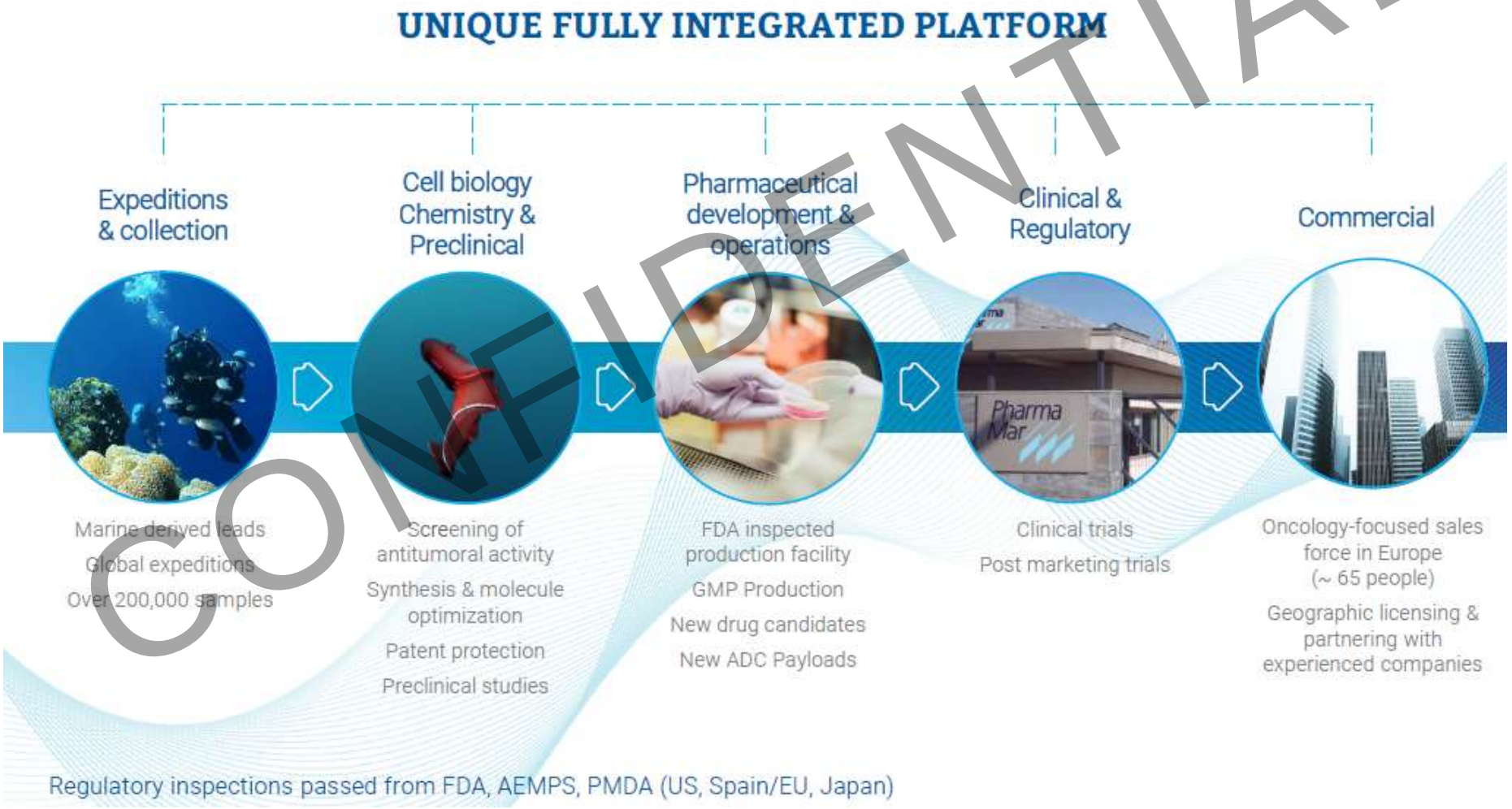
Established European Oncology Sales Force

Discovery Platform Strengthening Oncology Pipeline

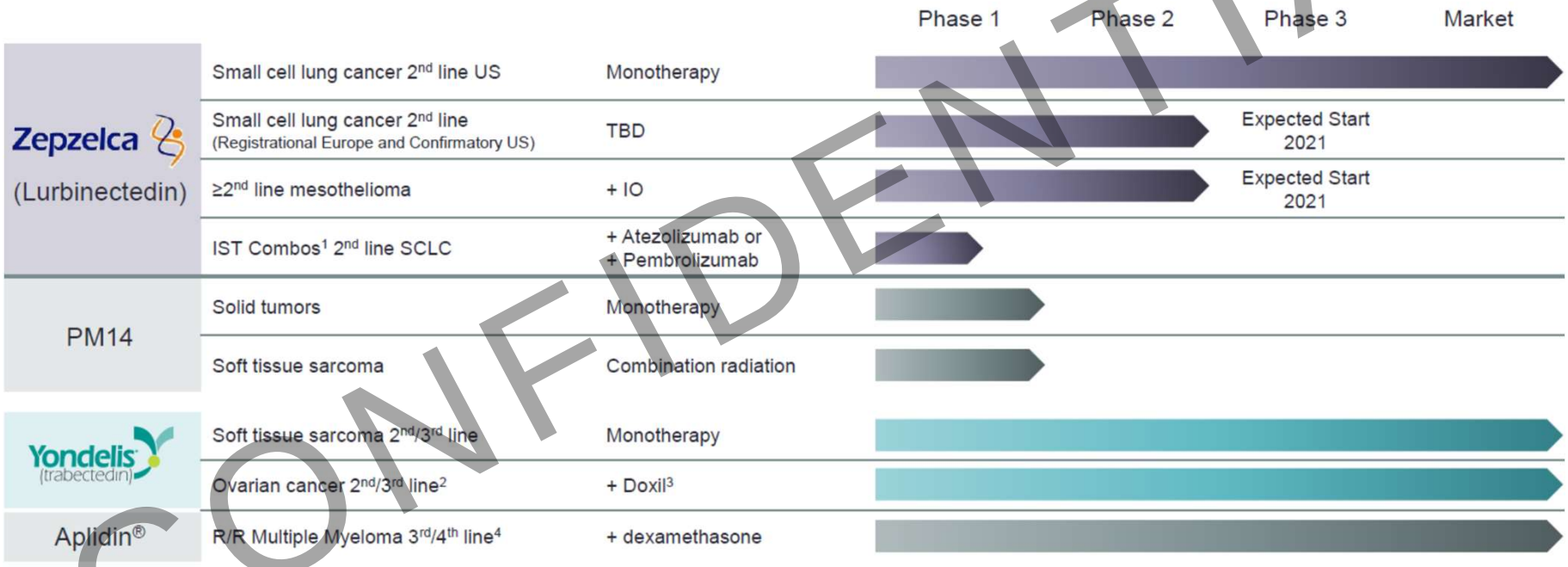
Diversified pipeline with late-stage asset and of 2 early-stage assets about to enter the clinic

Unique fully integrated platform

R&D capabilities to bring cancer drugs to the market



Oncology portfolio

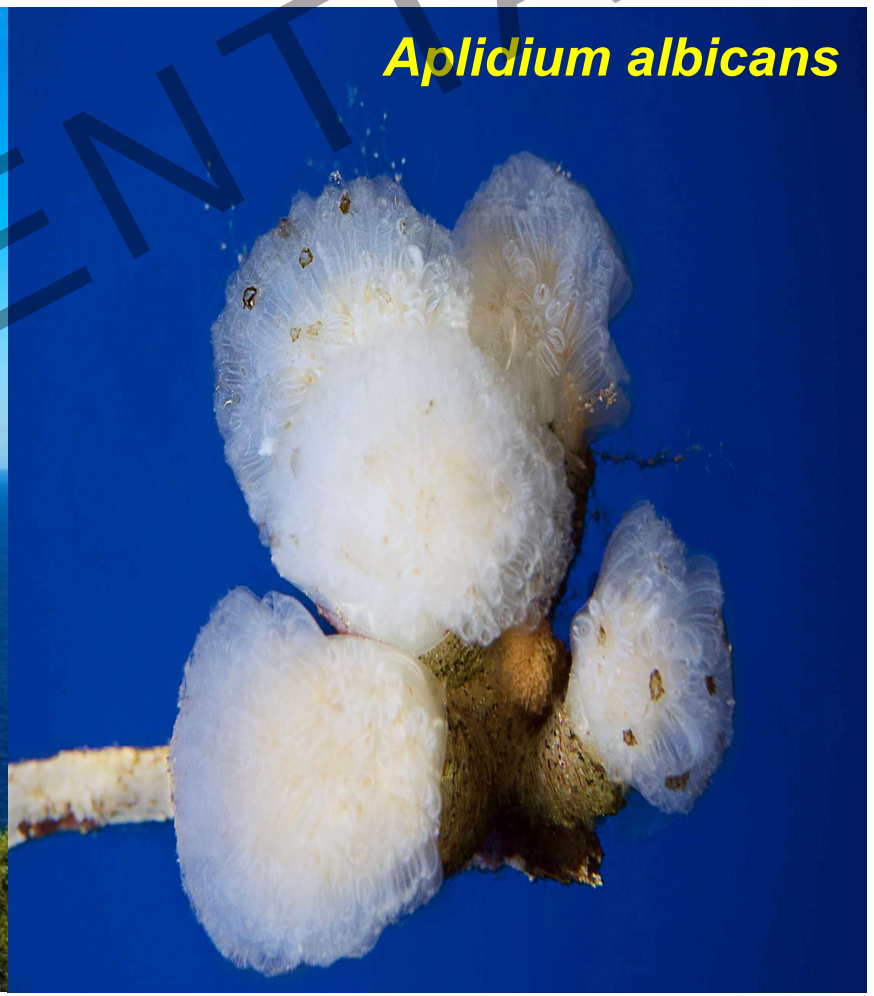


IST – Investigator Sponsored Trial
(1) Envisaged potential cohorts include Ewing's sarcoma, relapsed ovarian, 2nd line endometrial, pan small-cell (ex lung)
(2) Not approved in the USA
(3) Pegylated liposomal doxorubicin (PLD)
(4) Approved in Australia

Aplidin® (Plitidepsin)

Collection of *Aplidium albicans*

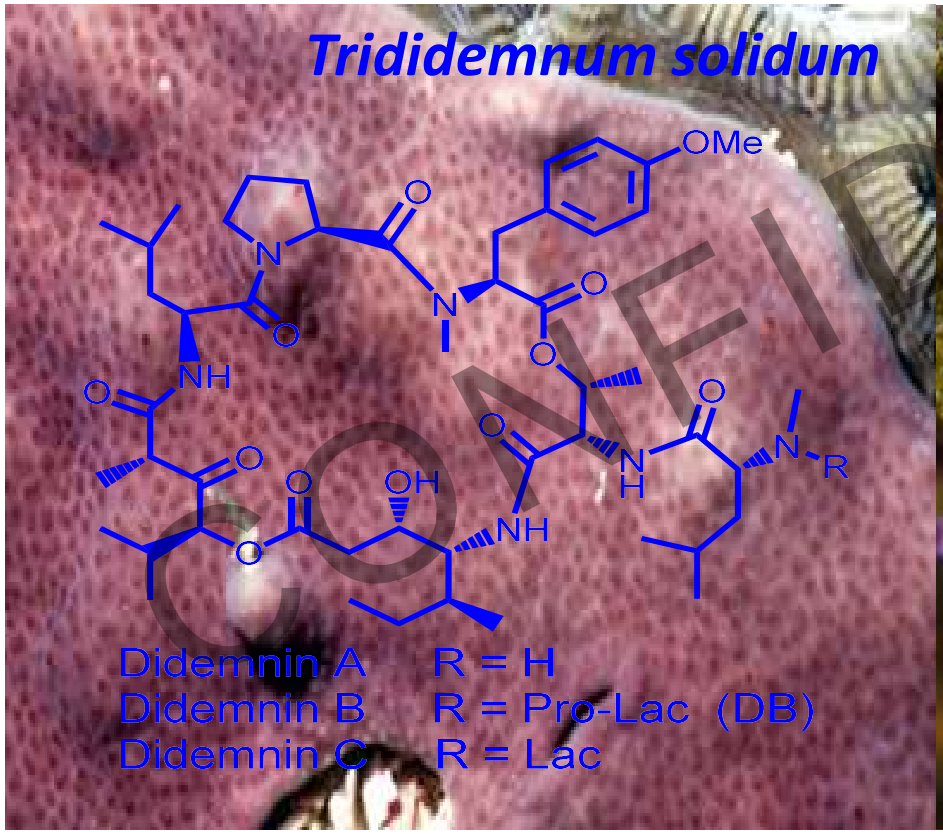
- ✓ *Aplidium albicans* was collected in 1988 and Aplidine was isolated in 1989



Aplidin® (Plitidepsin)

Chemical structure elucidated

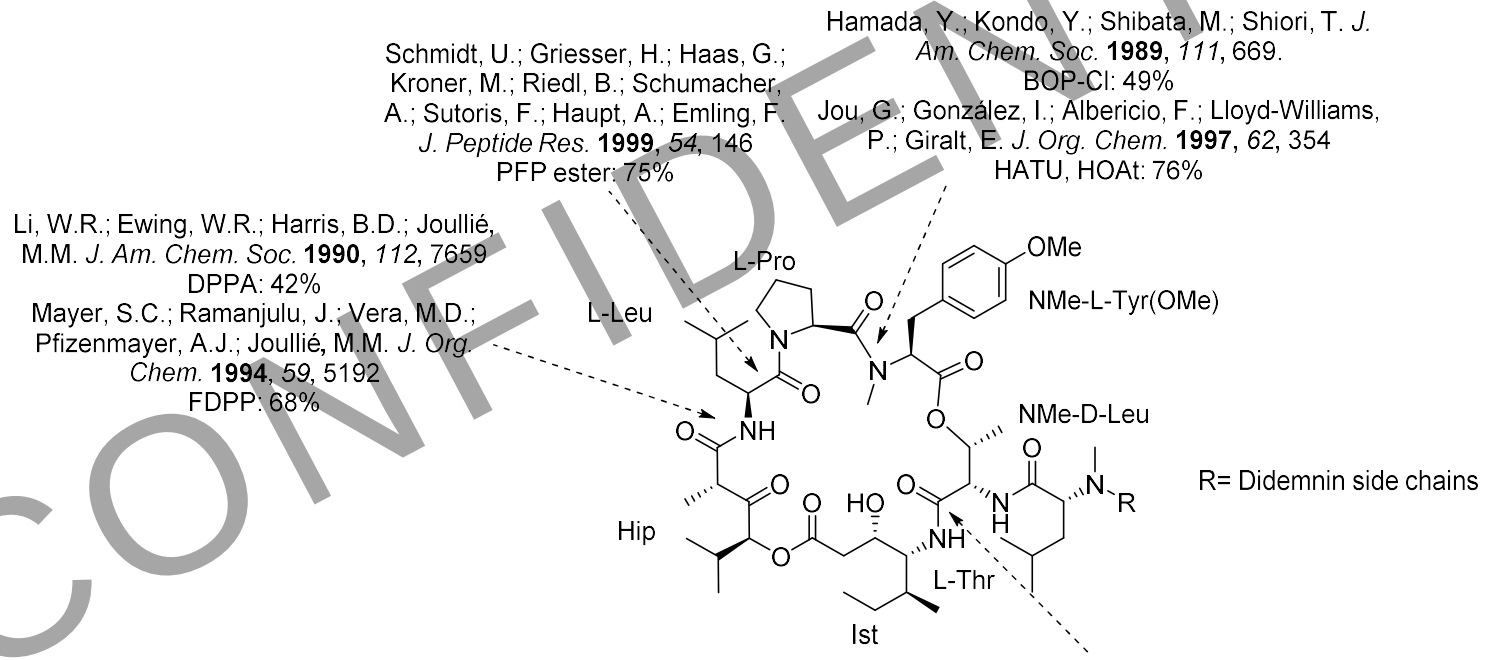
- Aplidine is a member of the class of compounds known as Didemnins
- Didemnin B was the first marine compound entering clinical trials



Aplidin® (Plitidepsin)

Solving of supply problem

Rinehart et al reported the first total synthesis of Didemnins in 1987. Subsequently, different research laboratories published several synthesis, differing mainly in the selection of the two amino acids to achieve macrocyclization (1989-1997).



Aplidin® (Plitidepsin)

In vivo effect of Aplidine in MM

Aplidine Synergizes with Bortezomib and Lenalidomide in MM Xenografts

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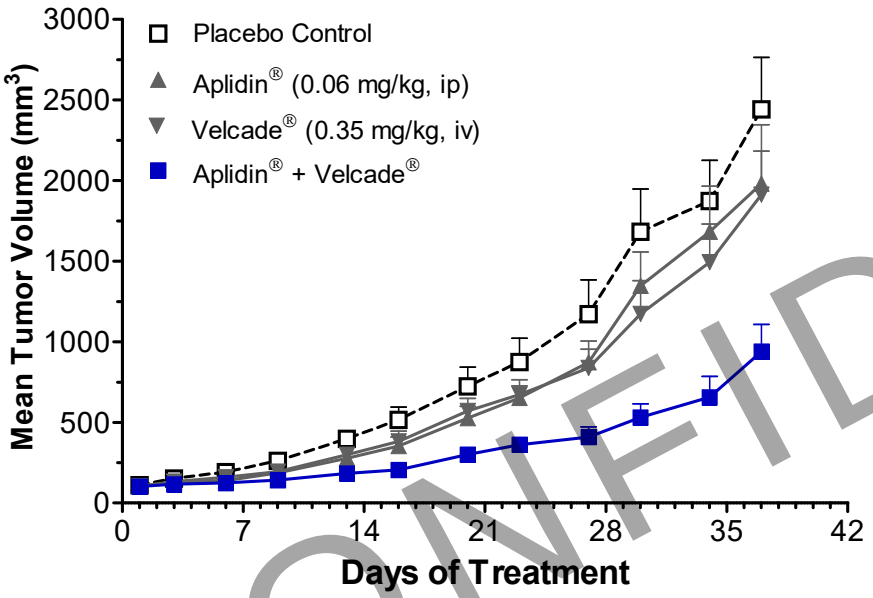
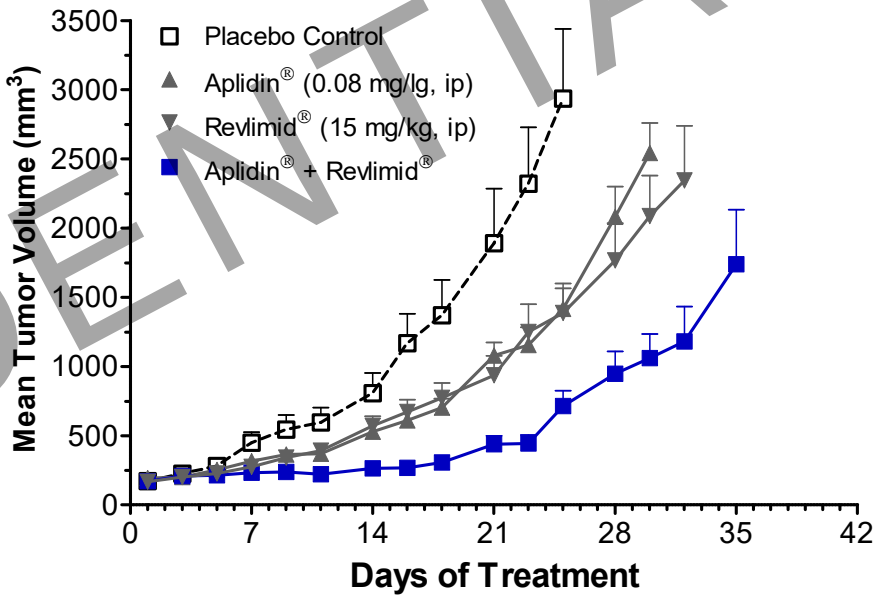
Aplidine + Velcade® (Bortezomib)



SCID mice bearing RPMI-8226 xenografts received

Aplidine: 9 Daily Dose & Velcade®: q3dx2

Aplidine + Revlimid® (Lenalidomide)



SCID mice bearing MM1S xenografts received

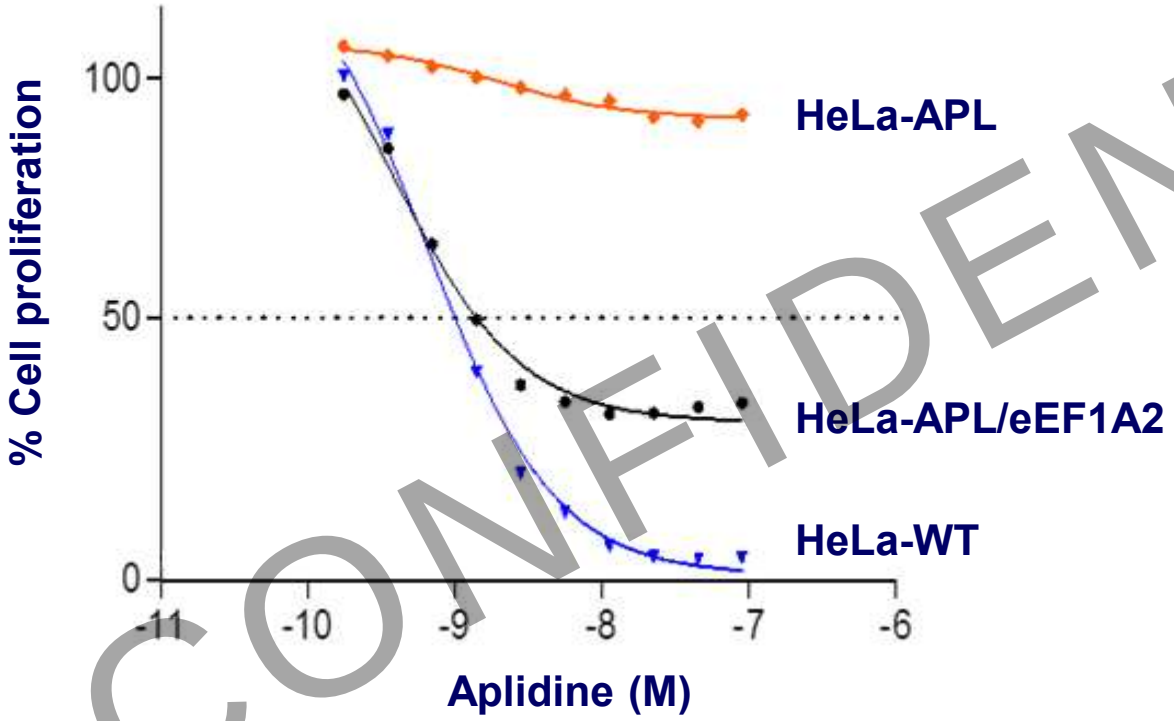
Aplidine: 5 Daily Dose/week & Revlimid®: 5 Daily Dose/week

Mitsiades *et al.* Aplidin, a Marine Organism-Derived Compound with Potent Antimyeloma Activity *in vitro* and *in vivo*. *Cancer Res.* **2008**, *68*, 5216–5225

Aplidin® (Plitidepsin)

Understanding the Mechanism of Action

eEF1A2 Sensitizes to Aplidine



- **Re-introduction of eEF1A2 sensitizes the resistant cells to Aplidine treatment**
- **Resistant cells recover intracellular signals induced by Aplidine**

Losada *et al.* Translation Elongation Factor eEF1A2 is a Novel Anticancer Target for the Marine Natural Product Plitidepsin. *Sci. Rep.* **2016**, *6*, 35100; doi: 10.1038/srep35100.

Aplidin® (Plitidepsin)

Phase II APL-B-014-03

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APL-B-014-03: Phase II Study with Aplidin® in Multiple Myeloma

Cancer Therapy: Clinical

Clinical Cancer Research

Phase II Clinical and Pharmacokinetic Study of Plitidepsin 3-Hour Infusion Every Two Weeks Alone or with Dexamethasone in Relapsed and Refractory Multiple Myeloma

María Victoria Mateos[1], Maria Teresa Cibeira[2], Paul G. Richardson[3], Felipe Prosper[4], Albert Oriol[5], Javier de la Rubia[6], Juan José Lahuerta[7], Ramón García-Sanz[1], Sonia Extremera[8], Sergio Szyldergemajn[8], Claudia Corrado[8], Harald Singer[8], Constantine S. Mitsiades[3], Kenneth C. Anderson[3], Joan Bladé[2], and Jesús San Miguel[1]

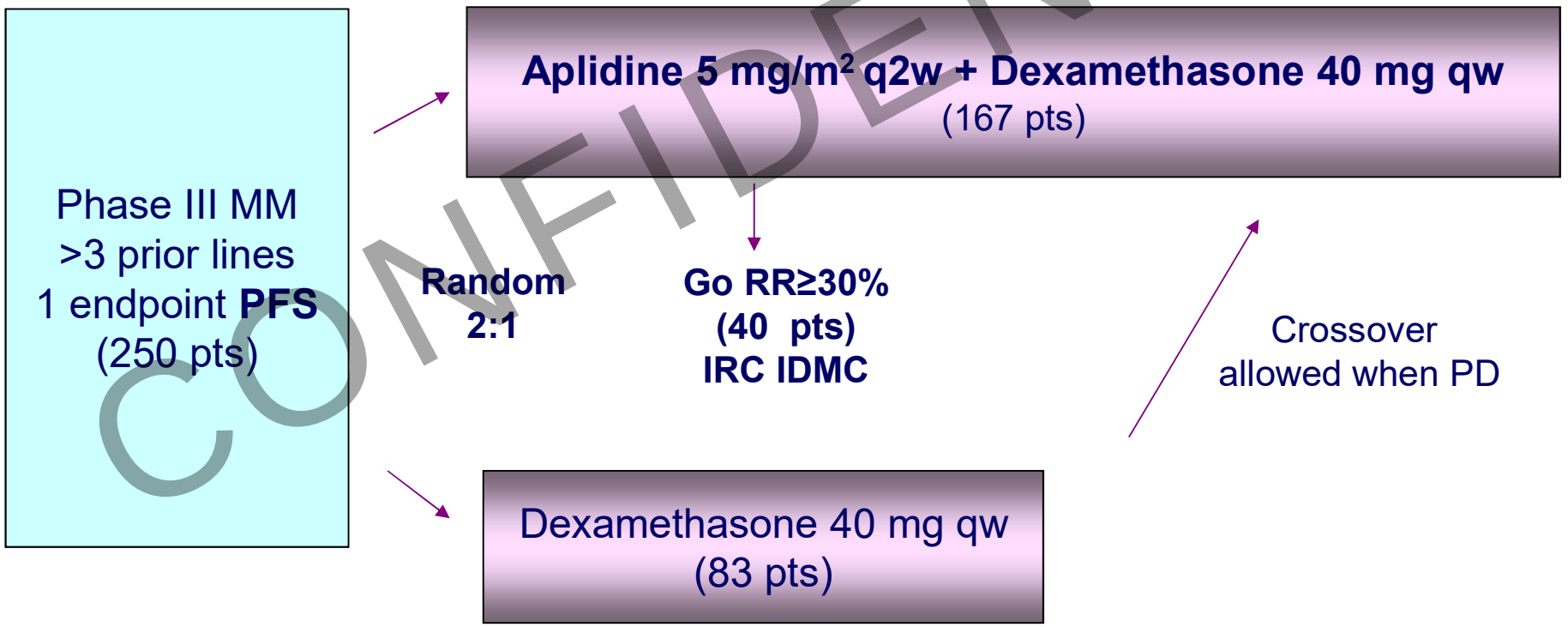
Clin Cancer Res. **2010**, *16*, 3260-3269

Aplidin® (Plitidepsin)

Phase III in Relapsed/Refractory Myeloma (ADMYRE)

Pharma Mar

Phase III Randomized Trial of Aplidine + Dexamethasone *vs* Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma



Aplidin® (Plitidepsin)

Phase III in Relapsed/Refractory Myeloma (ADMYRE)

Annals of Hematology (2019) 98:2139–2150
https://doi.org/10.1007/s00277-019-03739-2

ORIGINAL ARTICLE

Randomized phase III study (ADMYRE) of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma

Ivan Spicka[1] · Enrique M. Ocio[2] · Heather E. Oakervee[3] · Richard Greil[4] · Raymond H. Banh[5] · Shang-Yi Huang[6] · James M. D'Rozario[7] · Meletios A. Dimopoulos[8] · Sara Martínez[9] · Sonia Extremera[9] · Carmen Kahatt[9] · Vicente Alfaro[9] · Angelo M. Carella[10] · Nathalie Meuleman[11] · Roman Hájek[12] · Argiris Symeonidis[13] · Chang-Ki Min[14] · Paul Cannell[15] · Heinz Ludwig[16] · Pieter Sonneveld[17] · María Victoria Mateos[18,19]

Received: 9 January 2019 / Accepted: 12 June 2019 / Published online: 25 June 2019

Aplidin® (Plitidepsin)

Phase III in Relapsed/Refractory Myeloma (ADMYRE)

El CHMP confirma su tendencia de voto negativa para la comercialización de plitidepsina en Europa

- Se ha confirmado el anuncio que la compañía hizo el pasado 8 de noviembre, el CHMP de la EMA emite una opinión en contra de la aprobación de Aplidin® para el tratamiento del mieloma múltiple.

Madrid, 15 de diciembre de 2017. Tal y como se esperaba en el anuncio realizado por la Compañía el pasado 8 de noviembre[i], el Comité Europeo de Medicamentos de Uso Humano (CHMP, por sus siglas en inglés) ha emitido finalmente una opinión en contra de la aprobación de la solicitud de comercialización de Aplidin® (plitidepsina) para el tratamiento de los pacientes con mieloma múltiple en recaída, en combinación con dexametasona.

Aplidin® (Plitidepsin)

First Approval Australia December 2018

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	10 December 2018
Date of entry onto ARTG:	12 December 2018
ARTG number:	291661
Black Triangle Scheme	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Active ingredient:	Plitidepsin
Product name:	Aplidin
Sponsor's name and address:	Specialised Therapeutics Pharma Australia Pty Ltd PO Box 2299 Kew Victoria 3101 Australia
Dose form:	Powder for injection and solvent
Strength:	2 mg; after reconstitution, each mL of concentrate contains 0.5 mg of plitidepsin
Container:	Glass vial containing lyophilised powder (2 mg plitidepsin) and glass ampoule containing the diluent (4 mL).
Pack size:	One (1) vial and one (1) ampoule per carton
Approved therapeutic use:	*Aplidin, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator. Aplidin may be used after two prior lines of therapy if refractory and/or intolerant to both a proteasome inhibitor and an immunomodulator.*
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Aplidin is 5 mg/m^2 according to Body Surface Area (BSA).

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Australian Government

Department of Health

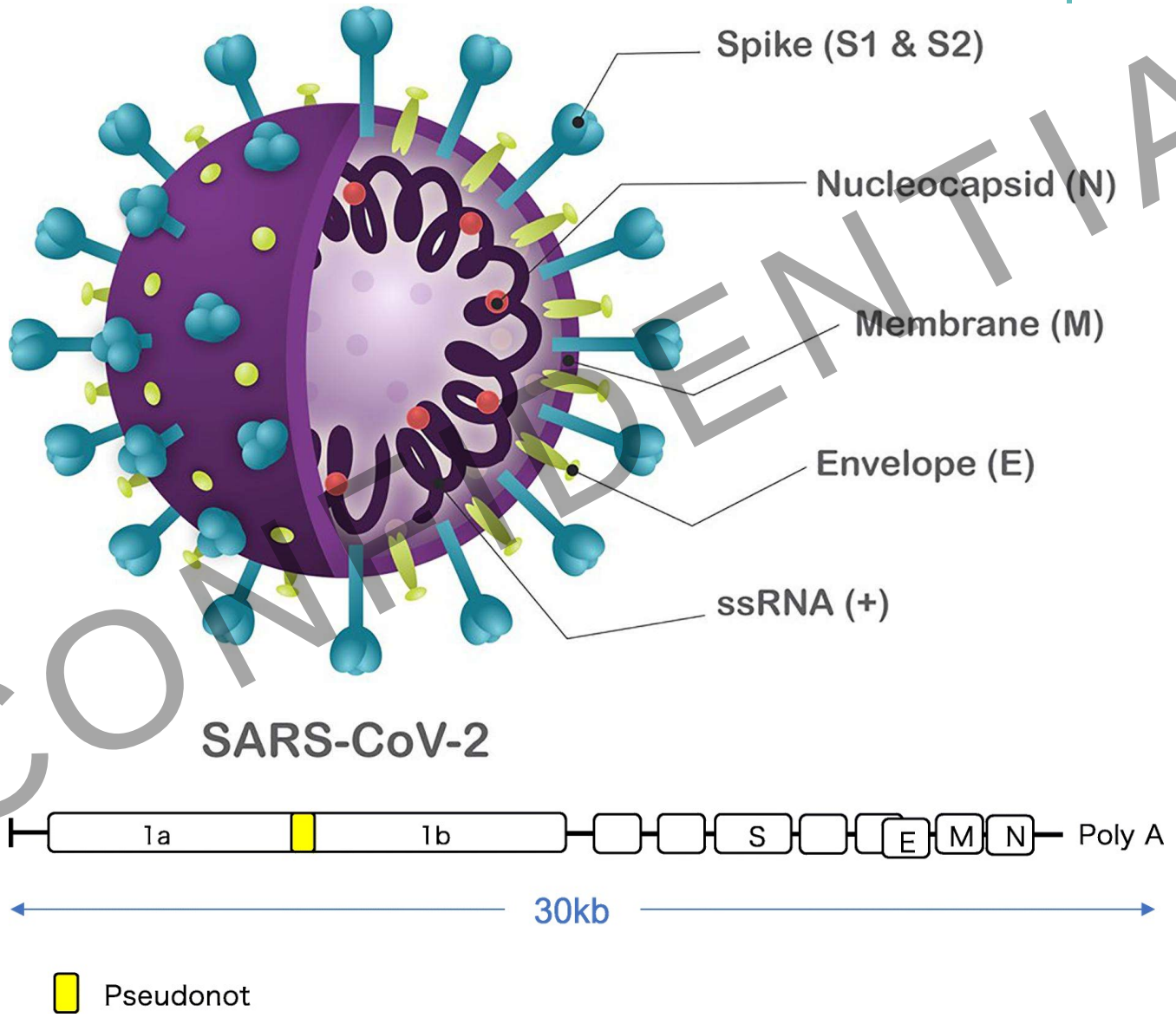
Therapeutic Goods Administration

Aplidin®

plitidepsin

COVID-19

Schematic diagram of the coronavirus structure and genomic structure



Drug repurposing

Table 1 | Selected successful drug repurposing examples and the repurposing approach employed

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	Zidovudine was the first anti-HIV drug to be approved by the FDA
Minoxidil	Hypertension	Hair loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Global sales for minoxidil were US$860 million in 2016 (Questale minoxidil sales report 2017; see Related links)
Sildenafil	Angina	Erectile dysfunction	1998	Retrospective clinical analysis	Marketed as Viagra, sildenafil became the leading product in the erectile dysfunction drug market, with global sales in 2012 of $2.05 billion[8]
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma	1998 and 2006	Off-label usage and pharmacological analysis	Thalidomide derivatives have achieved substantial clinical and commercial success in multiple myeloma
Celecoxib	Pain and inflammation	Familial adenomatous polyps	2000	Pharmacological analysis	The total revenue from Celebrex (Pfizer) at the end of 2014 was $2.69 billion (Pfizer 2014 financial report; see Related links)
Atomoxetine	Parkinson disease	ADHD	2002	Pharmacological analysis	Strattera (Eli Lilly) recorded global sales of $655 million in 2016
Duloxetine	Depression	SUI	2004	Pharmacological analysis	Approved by the EMA for SUI. The application was withdrawn in the US. Duloxetine is approved for the treatment of depression and chronic pain in the US
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of coexisting rheumatoid arthritis in patients with non-Hodgkin lymphoma treated with rituximab[144])	Global sales of rituximab topped $7 billion in 2015 (REF:[145])
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer. Worldwide sales of $237 million in 2015 (see Related links)
Fingolimod	Transplant rejection	MS	2010	Pharmacological and structural analysis[146]	First oral disease-modifying therapy to be approved for MS. Global sales for fingolimod (Gilenya) reached $3.1 billion in 2017 (see Related links)
Depoxetine	Analgesia and depression	Premature ejaculation	2012	Pharmacological analysis	Approved in the UK and a number of European countries; still awaiting approval in the US. Peak sales are projected to reach $750 million
Topiramate	Epilepsy	Obesity	2012	Pharmacological analysis	Qsymia (Vivus) contains topiramate in combination with phentermine
Ketoconazole	Fungal infections	Cushing syndrome	2014	Pharmacological analysis	Approved by the EMA for Cushing syndrome in adults and adolescents above the age of 12 years (see Related links)
Aspirin	Analgesia	Colorectal cancer	2015	Retrospective clinical and pharmacological analysis	US Preventive Services Task Force released draft recommendations in September 2015 regarding the use of aspirin to help prevent cardiovascular disease and colorectal cancer[33]

ADHD, attention deficit hyperactivity disorder; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MS, multiple sclerosis; SUI, stress urinary incontinence.

Nat. Rev. Drug. Discov. 2019, 18, 41–58.

COVID-19: Aplidin® (Plitidepsin)

Bibliography references

Department of Zoology and
Institute of Ecology,
University of Georgia, Athens 30602
ELEANORA IBERALL ROBBINS
U.S. Geological Survey,
Reston, Virginia 22092

References and Notes

1. Samples are from the Bandera Shale Member of the Ocoogah Formation and the Excello Shale Member of the Senora Formation collected from roadcuts east of Tulsa, Oklahoma; the Meade Peak Phosphatic Shale Member of the Phosphoria Formation collected from Mabie Canyon, Snowdrift Mountain, and Bloomington Canyon, Idaho, and Sublette Ridge and Coal Canyon, Wyoming; the Cumnock Formation collected from BMDH D-1 core hole from a depth of 156.7 m, north of Cumnock, North Carolina; and the Puente Formation collected from Union Oil Company well, Bell 107, in two samples between 3831 and 3957 m, Santa Fe Springs, California. For quantitative analysis, 10-g pieces of whole shale and nodules were treated at 22°C with 10 percent HCl for 24 hours, rinsed three times with distilled water, settled by gravity, and treated with 50 percent hydrofluoric acid for 24 hours. Samples were then rinsed five times with distilled water and passed through a 125-μm sieve and then a 25-μm sieve. Subsamples of the microfossil fraction were measured and counted at magnifications of 100 to 1000. Standard use of hot acid, centrifugation, hydroxide, and Shultze solution will destroy pellet remains. Thin sections of shale samples were examined qualitatively. The complete technique is described by E. I. Robbins and A. Traverse, in *Carolina Geologic Society Guidebook* (Savannah River Laboratory, Aiken, S.C., 1980), section B, p. 1.
2. Details of microfossil analyses, reconstructions of the paleoenvironments, and the economic importance of the formations are described by E. I. Robbins and K. G. Porter, in preparation.
3. H. A. Tourtelot, *Clays Clay Miner.* **27**, 313 (1979).
4. E. I. Robbins and K. G. Porter, *Palynology* **4**, 30 (1979).
5. Standard chemical analyses were performed by N. G. Skinner and Z. A. Hamlin, U.S. Geological Survey. The percent by weight of the intact pellet in the total sample was calculated by weighing the microfossil fraction (> 25 μm) and multiplying this weight by the intact pellet percent by volume.
6. R. E. Johannes and M. Satomi, *Limnol. Oceanogr.* **11**, 191 (1966).
7. S. Honjo, *J. Mar. Res.* **38**, 53 (1980).
8. J. T. Turner and J. C. Ferrante, *BioScience* **29**, 670 (1979); S. Honjo and M. R. Roman, *J. Mar. Res.* **36**, 45 (1978).
9. H. B. Moore, *J. Mar. Biol. Assoc. U.K.* **17**, 325 (1931); *ibid.*, p. 359; A. J. Iovino and W. H. Bradley, *Limnol. Oceanogr.* **14**, 898 (1969).
10. K. G. Porter, *Verh. Int. Ver. Theor. Angew. Limnol.* **19**, 2840 (1975); *Science* **192**, 1332

Didemnins: Antiviral and Antitumor Depsipeptides from a Caribbean Tunicate

Abstract. *Extracts of samples of a Caribbean tunicate (ascidian, sea squirt) of the family Didemnidae inhibit in vitro at low concentrations the growth of DNA and RNA viruses as well as L1210 leukemic cells. The active compounds isolated from the tunicate, didemnins A, B, and C, are depsipeptides, and didemnin B (a derivative of didemnin A) is the component active at the lowest concentration in inhibiting viral replication in vitro and P388 leukemia in vivo.*

We have isolated from a Caribbean tunicate a new class of depsipeptides, including highly active antiviral and antitumor agents (*1*). Although these depsipeptides—termed didemnins after the name of the tunicate family from which they are isolated—are closely related to one another, they vary in activity, suggesting the possibility of further chemical modification. This discovery confirms our earlier observations (*2*, *3*) that the subphylum Tunicata or Urochordata (phylum Chordata) is of special interest both for the chemistry and for the bioactivity of the compounds tunicates contain (*4*, *5*).

The tunicate in our study was collected at a number of sites (including Colombian, Honduran, Mexican, Belizean, and Panamanian waters) during the *Alpha Helix* Caribbean Expedition 1978 (AHCE 1978) (*3*). It has been assigned (*6*) to the family Didemnidae and is a member of the *Tridemnum* genus. Repeated tests of methanol-toluene (3:1) extracts of the didemnid on shipboard against herpes simplex virus, type 1, grown in CV-1 cells (monkey kidney tissue) indicated that it inhibited the growth of the virus, over and above an underlying cytotoxicity to the CV-1 cells. This result suggested that compounds in the tunicate extract offered promise both as antiviral agents and,

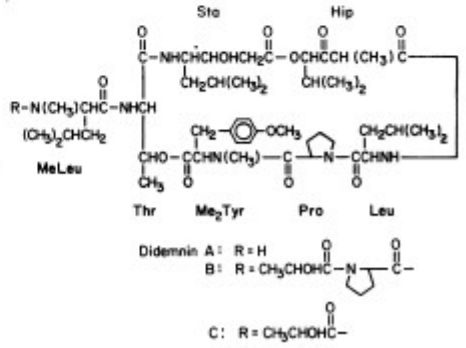


Fig. 1. Structures of didemnins.

COVID-19: Aplidin® (Plitidepsin)

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JOURNAL OF VIROLOGY, July 2008, p. 6962–6971
0022-538X/08/$08.00+0 doi:10.1128/JVI.00133-08

Vol. 82, No. 14

The Nucleocapsid Protein of Severe Acute Respiratory Syndrome Coronavirus Inhibits Cell Cytokinesis and Proliferation by Interacting with Translation Elongation Factor 1α▽

Bing Zhou,† Junli Liu,† Qiuna Wang, Xuan Liu, Xiaorong Li, Ping Li, Qingjun Ma, and Cheng Cao*

State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Biotechnology, Beijing 100071, China

Received 18 January 2008/Accepted 24 April 2008

Severe acute respiratory syndrome coronavirus (SARS-CoV) is the etiological agent of SARS, an emerging disease characterized by atypical pneumonia. Using a yeast two-hybrid screen with the nucleocapsid (N) protein of SARS-CoV as a bait, the C terminus (amino acids 251 to 422) of the N protein was found to interact with human elongation factor 1-alpha (EF1α), an essential component of the translational machinery with an important role in cytokinesis, promoting the bundling of filamentous actin (F-actin). In vitro and in vivo interaction was then confirmed by immuno-coprecipitation, far-Western blotting, and surface plasmon resonance. It was demonstrated that the N protein of SARS-CoV induces aggregation of EF1α, inhibiting protein translation and cytokinesis by blocking F-actin bundling. Proliferation of human peripheral blood lymphocytes and other human cell lines was significantly inhibited by the infection of recombinant retrovirus expressing SARS-CoV N protein.

ELSEVIER

Veterinary Microbiology
Volume 172, Issues 3–4, 27 August 2014, Pages 443-448

EF1A interacting with nucleocapsid protein of transmissible gastroenteritis coronavirus and plays a role in virus replication

Xin Zhang, Hongyan Shi, Jianfei Chen, Da Shi, Changlong Li, Li Feng

Division of Swine Infectious Diseases, National Key Laboratory of Veterinary Biotechnology, Harbin Veterinary Research Institute of the Chinese Academy of Agricultural Sciences, Harbin 150001, China

COVID-19: Aplidin® (Plitidepsin)

In vitro & *in vivo* activity

Science
AAAS

Cite as: K. M. White *et al.*, *Science*
10.1126/science.abf4058 (2021).

Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A

Kris M. White[1,2*†], Romel Rosales[1,2*], Soner Yildiz[1,2], Thomas Kehrer[1,2], Lisa Miorin[1,2], Elena Moreno[1,2], Sonia Jangra[1,2], Melissa B. Uccellini[1,2], Raveen Rathnasinghe[1,2], Lynda Coughlan[3], Carles Martinez-Romero[1,2], Jyoti Batra[4,5,6,7], Ajda Rojc[4,5,6,7], Mehdi Bouhaddou[4,5,6,7], Jacqueline M. Fabius[4,6], Kirsten Obernier[4,5,6,7], Marion Dejosez[8], María José Guillén[9], Alejandro Losada[9], Pablo Avilés[9], Michael Schotsaert[1,2], Thomas Zwaka[8], Marco Vignuzzi[10], Kevan M. Shokat[4,6,7,11], Nevan J. Krogan[1,4,5,6,7†], Adolfo García-Sastre[1,2,12,13†]

[1]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [2]Global Health Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Department of Microbiology and Immunology and Center for Vaccine Development and Global Health (CVD), University of Maryland School of Medicine, Baltimore, MD, USA. [4]Quantitative Biosciences Institute (QBI), University of California, San Francisco, CA 94158, USA. [5]J. David Gladstone Institutes, San Francisco, CA 94158, USA. [6]QBI Coronavirus Research Group (QCRG), San Francisco, CA 94158, USA. [7]Department of Cellular and Molecular Pharmacology, University of California, San Francisco, CA 94158, USA. [8]Huffington Foundation Center for Cell-Based Research in Parkinson's Disease, Department for Cell, Regenerative and Developmental Biology, Black Family Stem Cell Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [9]Research and Development Department, PharmaMar, 28770 Colmenar Viejo, Madrid, Spain. [10]Viral Populations and Pathogenesis Unit, CNRS UMR 3569, Institut Pasteur, 75724 Paris Cedex 15, France. [11]Howard Hughes Medical Institute, University of California, San Francisco, CA 94143, USA. [12]Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [13]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

*These authors contributed equally to this work.

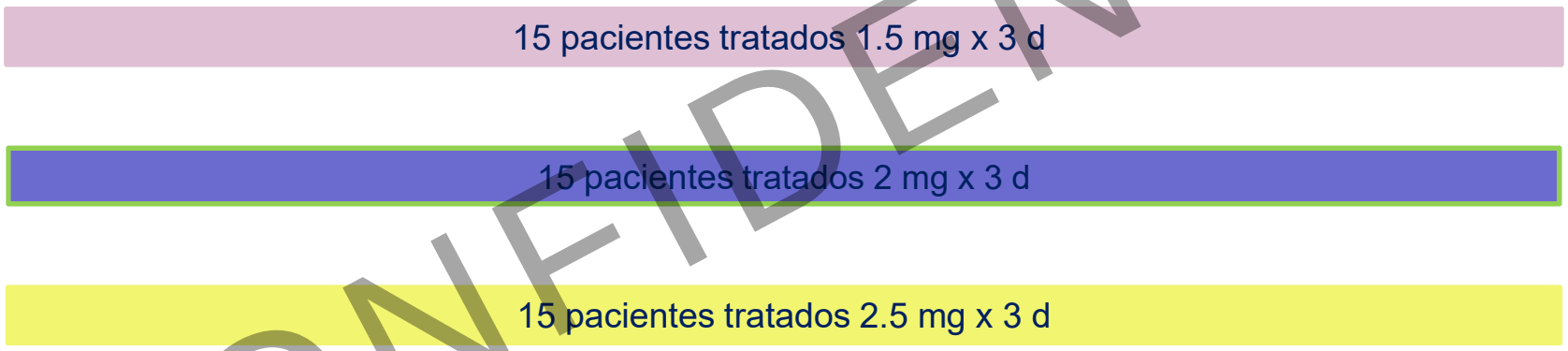
†Corresponding author. Email: kris.white@mssm.edu (K.M.W.); nevan.krogan@ucsf.edu (N.J.K.); adolfo.garcia-sastre@mssm.edu (A.G.-S.)

SARS-CoV-2 viral proteins interact with the eukaryotic translation machinery and inhibitors of translation have potent antiviral effects. Here we report that the drug plitidepsin (aplidin), which has limited clinical approval, possesses antiviral activity (IC_{90} = 0.88 nM) 27.5-fold more potent than remdesivir against SARS-CoV-2 in vitro, with limited toxicity in cell culture. Through the use of a drug resistant mutant, we show that the antiviral activity of plitidepsin against SARS-CoV-2 is mediated through inhibition of the known target eEF1A. We demonstrate the in vivo efficacy of plitidepsin treatment in two mouse models of SARS-CoV-2 infection with a reduction of viral replication in the lungs by two orders of magnitude using prophylactic treatment. Our results indicate that plitidepsin is a promising therapeutic candidate for COVID-19.

COVID-19: Aplidin® (Plitidepsin)

APLICOV Phase I-II

46 pacientes reclutados
45 pacientes tratados
Solo hospitales españoles



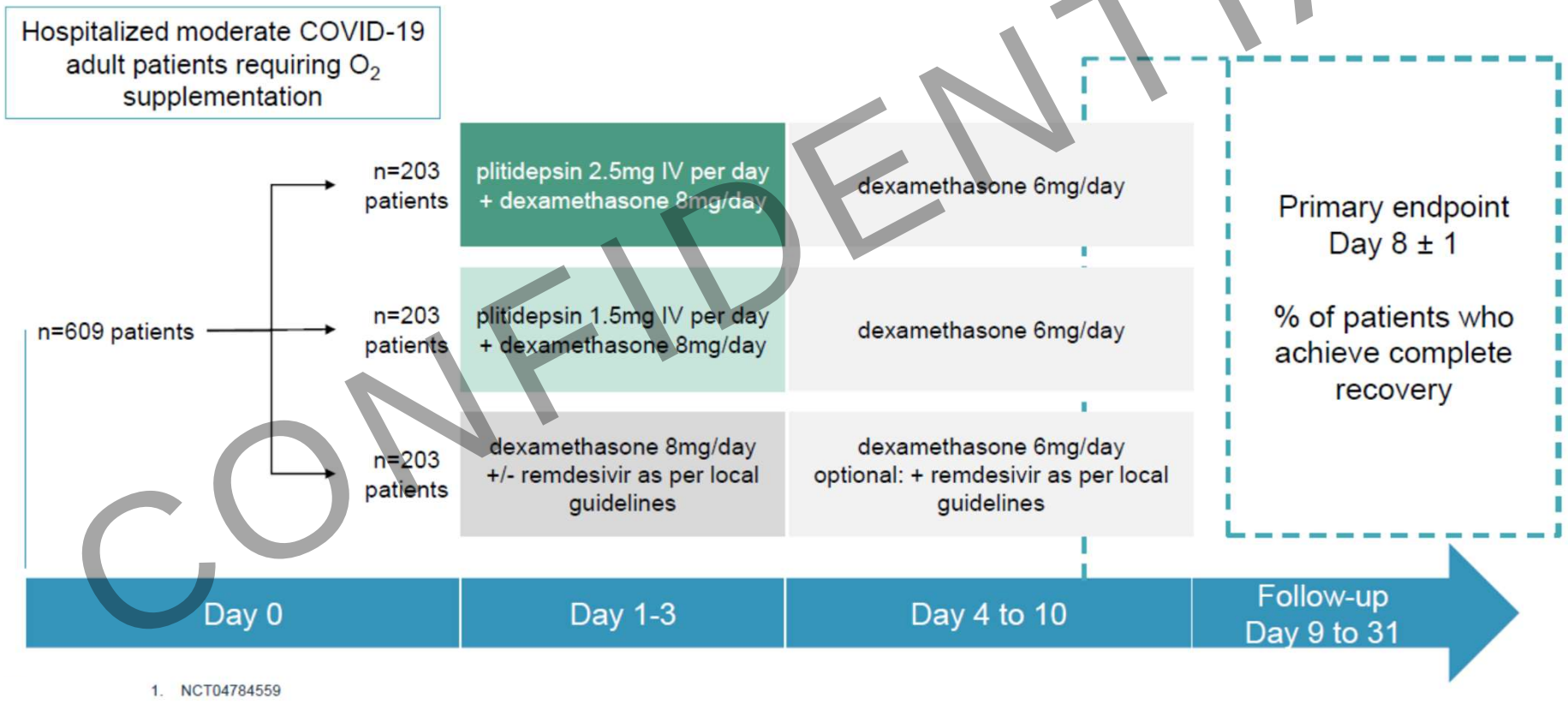
Resultado del estudio: POSITIVO

Plitidepsin has a positive therapeutic index in adult patients with COVID-19 requiring hospitalization
https://www.medrxiv.org/content/10.1101/2021.05.25.21257505v1

COVID-19: Aplidin® (Plitidepsin)

NEPTUNO Phase III

Plitidepsin COVID-19 Phase 3[1] Study Design in COVID-19 Adult Patients with Moderate Disease



1. NCT04784559

www.pharmamar.com

Andrés Francesch

Procesos Químicos Farmacéuticos, I+D

afrancesch@pharmamar.com

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European Regional Development Fund

EUROPEAN UNION

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