Genovate Biotechnology Co., Ltd.
健亞生物科技股份有限公司

December 26, 2018

Company Overview

- Genovate is a fully integrated specialty pharmaceutical company focusing on new drug development and equipped with PIC/S GMP manufacturing, marketing and distribution capabilities.
- Major Investors:
  - National Development Fund, Executive Yuan (26.54%)
  - Chinachem Group (HK) (10.95%)
- Established: 1993
- Number of Employees: 167
- Paid-in Capital: US$35M
- Revenue: US$11.5M (Q3/2018)
- Major Partners:
  - Medeor – Cellular immunotherapy; Jointly develop MDR-101 in Asia
  - SyneuRx – CNS disorders; Responsible for CMC of NaBen® (2 BTDs)
  - NaviFUS – BBB opening; Jointly develop CNS indications

Major Milestones (2013-2018)

2013	Invests in SyneuRx (TPEx:6575) who receives two “Breakthrough Therapy Designations“ from the US FDA in 2014 (SND13) and 2015 (SND12).
2013	Invests in Reber , TheVax with lead program of HPV therpapeutic vaccine, and PuraPharm (HKEx:1498) majored in concentrated Chinese medicine granules and invented Nong’s® clinic providing a total solution in Chinese medicine dispensary system.
2014	Invests in UniPharma (TPEx:6621) specialized in diagnostics and devices.
2015	Invests in Medeor Therapeutics specialized in cellular immunotherapy.
2016	Invests in NaviFUS dedicated in providing solutions to crossing BBB.
2017	Invests in Soleno (NASDAQ:SLNO) with lead program addressing PWS and GenVax specialized in formulation development.
2017	Completes IND application and initiates clinical development of PMR in the US.
2018	Obtains NDA approval of Mycocep for the new indication in the induction and maintenance therapy of lupus nephritis in Taiwan.

GMP Manufacturing (1/2)

- Area of the site: 11,700 m^2
- Area of the manufacturing facility: 6,700 m^2
- Area of the warehouse: 1,700 m^2
- Area of the testing laboratory: 460 m^2

Capabilities	Capacity (per day)
Tablet	1,310,000 Tabs
Film Coating, Sugar Coating	
Capsule	200,000 Caps
Injection Liquid	
Less than 10 cc Dosage	~ 20,000 Vials
Less than 10 cc Dosage	~ 40,000 Ampoules
Bigger Size to 100cc Dosage	~ 360L
Blister PKG/Al-Al PKG Line	1,200,000 Tabs/Caps

GMP Manufacturing (2/2)

- **Accreditation**

  2007 AFM by Japanese MHLW for non-sterile and sterile products

  2008 GMP accredited by Korean MFDS

  2010 PIC/S GMP accredited by TFDA and sterile ophthalmic solutions line added in 2014.

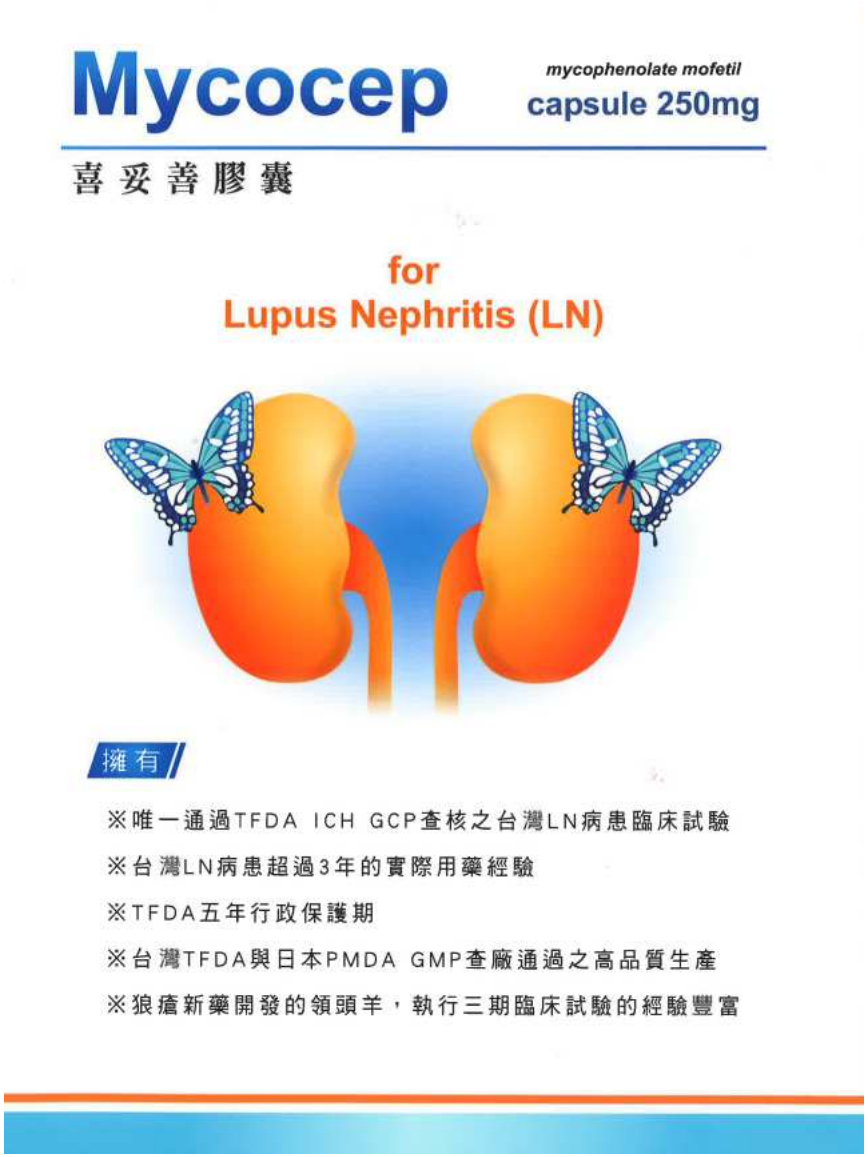
  2018 PIC/S GMP accredited by Japanese PMDA

- **Development and manufacture of proprietary products**
  - **New drugs, such as Genetaxyl™ (patented new formulation of Paclitaxel), Robatrol™ (Ribavirin capsule marketed by Roche), Linicor™ (Niacin ER/Lovastatin marketed by TSH), Mycostatin™ (Nystatin powder for oral solution).**
  - **Niche generic drugs, injectable preparation such as Atracurium, Rocuronium, and Cisatracurium as adjunct to general anaesthesia and ophthalmic solutions such as Bimatoprost、Latanoprost、Dorzolamide for glaucoma treatment.**
- **Professional contract manufacturing services**
  - **Major clients including DSTW, TSH, etc.**
- **Professional contract development and manufacturing services**
  - **Major clients including SyneuRx (NaBen®), UIC Group (Bowklean™ - Sodium Picosulfate/Magnesium Oxide/Anhydrous Citric Acid), etc.**
- **Drug export to Korea and southeast Asia since 2003.**

New Indication New Drug Mycocep™

- New indication of Mycocep (Mycophenolate Mofetil, MMF) in the induction and maintenance therapy of Lupus Nephritis (LN).
- There are approximately 30,000 SLE patients in Taiwan. The prevalence of renal disease requiring medical evaluation and treatment is about 49% in Chinese patients with SLE after 5 years of initial diagnosis.
- MMF is recommended by the ACR guidelines (2012) for the treatment and management of LN. Based on its better treatment outcome in terms of time to treatment failure and its less severe adverse events compared to azathioprine (AZA) treatment, MMF has emerged as the first-line standard-of-care therapy for both inducing and maintaining improvement of LN in recent year.
- The NDA-enabling study comparing Mycocep™ versus AZA for maintenance therapy of LN has been completed, inspected and accepted by TFDA in Feb-2018.
- Over 90% of study subjects are currently undergoing “compassionate therapy” after the study.
- Taiwan NDA approval was granted in Sep-2018.

Mycocep capsule 250mg 喜妥善膠囊



雙重感染B、C肝病毒的病人，如何治療？

- 台灣在世界上是屬於B、C肝高盛行的地區，B型肝炎帶原者約250萬人，C型肝炎病患也約有30~45萬人，其中身上同時帶有B肝及C肝病毒更有13萬至26萬之多。當體內B、C肝炎「共舞」時，該如何治療？需要先殲滅哪一隻病毒呢？
- 在台灣，大多數人是先得到B型肝炎，之後再感染C型肝炎，不過仍有少數人是相反或是同時感染兩種病毒，所以在大多數雙重感染的病人中，C型肝炎病毒大致上是較強勢的病毒，且可確定的是，感染兩種病毒對肝的傷害確定比感染單一病毒時的傷害更大。
- 目前使用治療C型肝炎藥物在治療B型與C型肝炎雙重感染的病人時，對C型肝炎病毒的療效與單純感染C型肝炎者一樣好。不過當C型肝炎病毒被消除或壓抑時，B肝病毒可能趁機大量複製而持續造成肝炎。因此在治療雙重感染的病人方面，仍有待更進一步的研究。
- 台灣臨床試驗研究聯盟（Taiwan Clinical Trial Consortium）的肝病組（主持人：臺大劉俊人教授）在科技部經費補助下，正在八家教學醫院執行一項有創意且先進的有關使用治療C肝藥物（DAAs：Direct-Acting Antivirals）與治療B肝藥物（Livepro 利甘平）治療雙重感染B、C肝病毒病人的臨床試驗（主持人：成大鄭斌男教授），希望能找到最佳良方。

New Formulation New Drug PMR

- Patented “once-a-day” modified-release of Cilostazol for the treatment of Intermittent Claudication (IC).
- The global market of IC treatments is over US$500M and about US$18B for antiplatelet treatments. The global sales of Cilostazol is about US$250M.
- Taiwan pharmacokinetic study showed that in comparison to Ciloslazol bid, PMR had
  - Lower Cmax
  - Lower Cmax/Cmin ratio
  - Lower area under the plasma concentration time curve (AUC)
- Taiwan PhII study nicely demonstrated the trend of better efficacy and safety profile (including less headache, diarrhea and palpitation, the leading causes of treatment discontinuation) comparing to Cilostazol bid.
- US IND has been successfully filed and the clinical development is ongoing.

2017年Cilostazol IR 台灣市場約有2.9億元(NTD)

藥品分類分組名稱	2014年申報量	2015年申報量	2016年申報量	2017年申報量
CILOSTAZOL, 一般錠劑膠囊劑，50.00MG	19,751,706	18,313,441	17,364,695	17,643,867
CILOSTAZOL, 一般錠劑膠囊劑，100.00MG	7,238,157	8,478,151	10,098,005	12,102,673

Cilostazol 50mg NHIP 7.0元（6家）
Cilostazol 100mg NHIP 13.7元（5家）

2.1.1.5. Cilostazol（如Pletaal）：(90/6/1、100/7/1、104/4/1、105/5/1)

1. 使用於無休息時疼痛及周邊組織壞死之間歇性跛行病人（周邊動脈疾病Fontaine stage II），用於增加最大及無痛行走距離。
2. 經生活模式改變及其他治療後，仍無法充分改善間歇性跛行症狀病人之二線治療。
3. 用於無法耐受acetylsalicylic acid且屬非心因性栓塞之腦梗塞患者，以預防腦梗塞之再復發，並符合下列條件之一(105/5/1)：
   (1) 對acetylsalicylic acid過敏。
   (2) 臨床診斷確定爲acetylsalicylic acid所導致之消化性潰瘍或上消化道出血、穿孔病史者。需於病歷註明發生時間。
   (3) 最近一年內臨床診斷確定爲消化性潰瘍者。病歷上應有明確消化性潰瘍之典型症狀紀錄及發病時間。
   (4) 最近一年內經上消化道內視鏡檢查或上消化道X光攝影檢查證實消化性潰瘍或發生上消化道出血、穿孔病史。需於病歷註明上消化道內視鏡或上消化道X光攝影檢查時間。但對acetylsalicylic acid無法耐受，且身體狀況無法忍受內視鏡或消化道X光攝影檢查者（如75歲(含)以上罹有中風或長期卧床者）不在此限。

Cilostan CR Tab. Of Korea United Pharm. Inc., started clinical trials in China

Clinical trials were approved by CFDA following technology transfer

Cilostan CR Tab. of Korea United Pharm.Inc.(KUP, CEO Duk Young Kang) was approved for clinical trials(Phase 1 and 2) by CFDA(China Food and Drug Administration)

Cilostan CR Tab., which is one of Incrementally Modified Drug(IMD) and was released in 2013 after R&D for 5 years by KUP, shows significant improvement in patient compliance by taking once a day.

Cilostan CR Tab. consists of 2 layers immediate release layer and sustained release layer. It shows sustained plasma concentration for 24 hours through the Double Controlled-Release System, which KUP obtained patent from Korea and China.

KUP made a contract for technology transfer of Cilostan CR Tab. and Clanza CR Tab. with Jiangxi Jimin Kexin Pharmaceutical (JJK) in June, 2013. The value of the contract is US$69million.

JJK and KUP started licensing procedure of Clanza CR Tab. and Cilostan CR Tab. with CFDA. They passed verification test for pharmaceutical product and obtained approval for clinical trials from CFDA. JJK will conduct clinical trials(Phase 1 and 2) for Cilostan CR Tab. in China and it will take approximately 2 years. According to CFDA's regulations, final licensing will be done once the clinical trials are successful.

KUP was awarded for Technology of Developing New Drug (Cilostan CR Tab.) at the 16th Korea New Drug Award ceremony in Feb., 2015. By recording over 10 billion (KRW) sales for Cilostan CR Tab. in 2015, Cilostan CR Tab. is regarded as the 1st blockbuster product of KUP.

研發策略之股權投資（1/2)

持有之公司	營業項目	持股比例	健亞合作項目
昌達生化科技	醫藥研發與技術委辦服務之公司(CRO)	6.33%	臨床委託
心悅生醫 (興櫃/6575)	中樞神經系統新藥開發	5.94%	劑型開發與生產製造
瑞寶基因	動物疫苗	1.00%	無
生控基因	子宮頸癌與B肝治療型疫苗	0.54%	HPV Vx 中國開發
Purapharm (HKEX/1498)	中藥研究生產與銷售	0.83%	多醣體研發

研發策略之股權投資（2/2)

持有之公司	營業項目	持股比例	健亞合作項目
Medeor Therapeutics	免疫細胞治療	2.38%	亞洲換肝
Soleno Therapeutics (NASDAQ/SLNO)	開發治療小胖威力症候群	1.08%	區域市場
華宇藥品 (興櫃/6621)	護肝新藥與高階醫療器材	17.7%	劑型開發與生產製造
浩宇生醫	聚焦式超音波腦部藥物釋放系統	13.7%	神經退化（區域）
Genovate-NaviFUS Inc.	投資	50%	腦神經相關疾病新療法（澳洲）

核心優勢與策略佈局

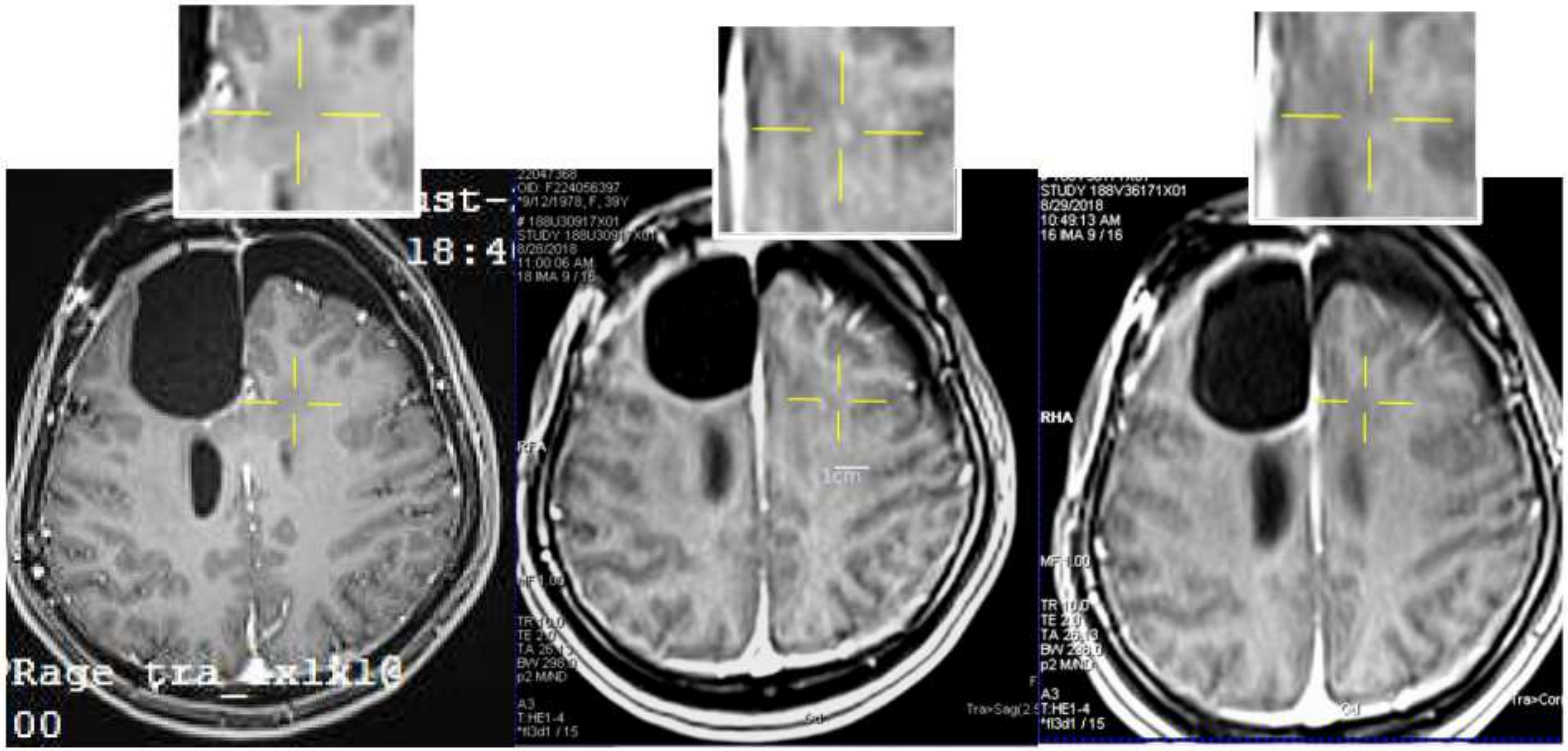
- 核心優勢
  - 核心技術：劑型改良、配合工廠生產（心悅、華宇）
  - 優勢利基：選題靈活、搭配投資、取得合作商機（心悅、生控）
  - 市場應用：經臨床驗證後，進行區域授權或市場銷售（DBPR108、Mycocep）
  - 國際競爭力：依各計畫屬性，規劃不同的開發策略（PuraPharm、浩宇、Medeor）
- 策略佈局
  - PMR：2019美國NDA，成功後尋求國際授權。
  - 心悅：全力配合兩個「BTDs」計畫的時程，提供CMC相關專業。
  - 浩宇：合作開發CNS疾病新療法，預計1H/2019展開臨床試驗。
  - Soleno：評估區域市場，銷售合作。
  - 華宇：共同合作新藥計畫，提供CMC相關專業。

Clinical Trial I： BBB open/ rGBM

- **Planning**
  - NaviFUS initiaed, IDE safety/ feasibility clinical trial
  - 2018.01 TFDA approval
  - 2018.04 IRB approval
  - 2018.08 2 patients recruited for level I
  - 2018.09 DSMB meeting I
  - 2018.11 2 patients recruited for level II
  - 2019.1 DSMB meeting II
  - Wish to finish it in 2019/Q1

2nd Patient conduct FUS-BBB opening

CE-T1



Pre FUS | 0.5hr Post FUS | 24 hrs Post FUS

Clinical Trial II： BBB opening/ rGBM

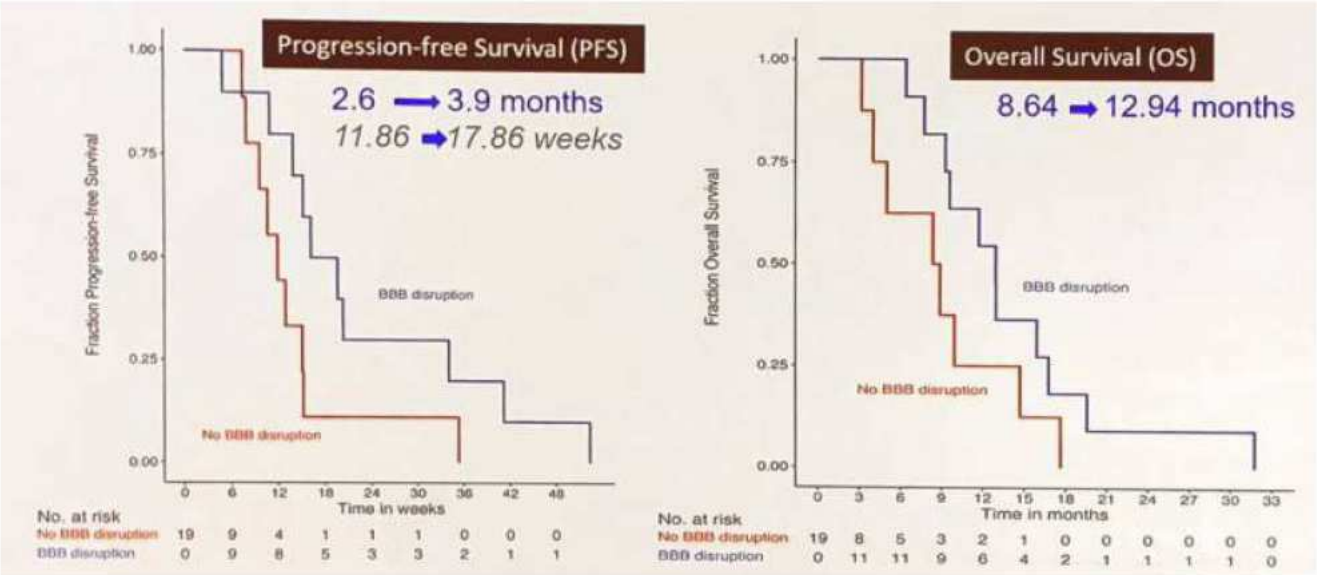
- **Planning**
  - **Avastin:**
    - **In rGBM, Avastin+FUS**
    - **CDE consultation on 12/05**
  - **IRESSA/ Tagrisso:**
    - **In LCBM, TKI drug + FUS**
    - **Pre-Clinical data collection**

回覆2018/10/02 審查意見- 2-6

SonoCloud (CarThera) Phase I/II in rGBM

Ultrasound + Carboplatin (Oct. 21-25, 2018 FUS Symposium 2018)

Efficacy

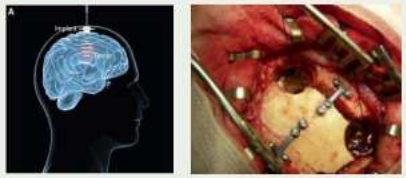


Safety

- Device-related SEAs were transient and manageable
- No “Dose-limiting toxicity (DLT)” related to the trial

回覆2018/10/02 審查意見-2-6

Clinical Activities in FUS-BBB Opening

公司名稱	CarThera	InSightec	浩宇生醫
產品名稱	SonoCloud	ExAblate	NaviFUS
產品圖示			
臨床進度	**US + Carboplatin** 法國第1個Phase I/II完成； 第2個Phase I/II 預計2018/12開始	**FUS + chemotherapy** 加拿大、韓國及美國Trials收案中	**FUS only** *需加藥試驗追上 CarThera & InSightec 台灣Phase I 收案中 (已完成3例)
侵入式治療	高侵入性	非侵入性(但須使用頭釘固定)	非侵入性
超音波系統	非聚焦式	聚焦式	聚焦式
開啟BBB位置	無選擇性	局部	局部
導引系統	無	MRI系統	手術導航系統
每次使用時間	1小時	4小時	0.5小時

BBB open/AD or Neuromodulation/ Epilepsy

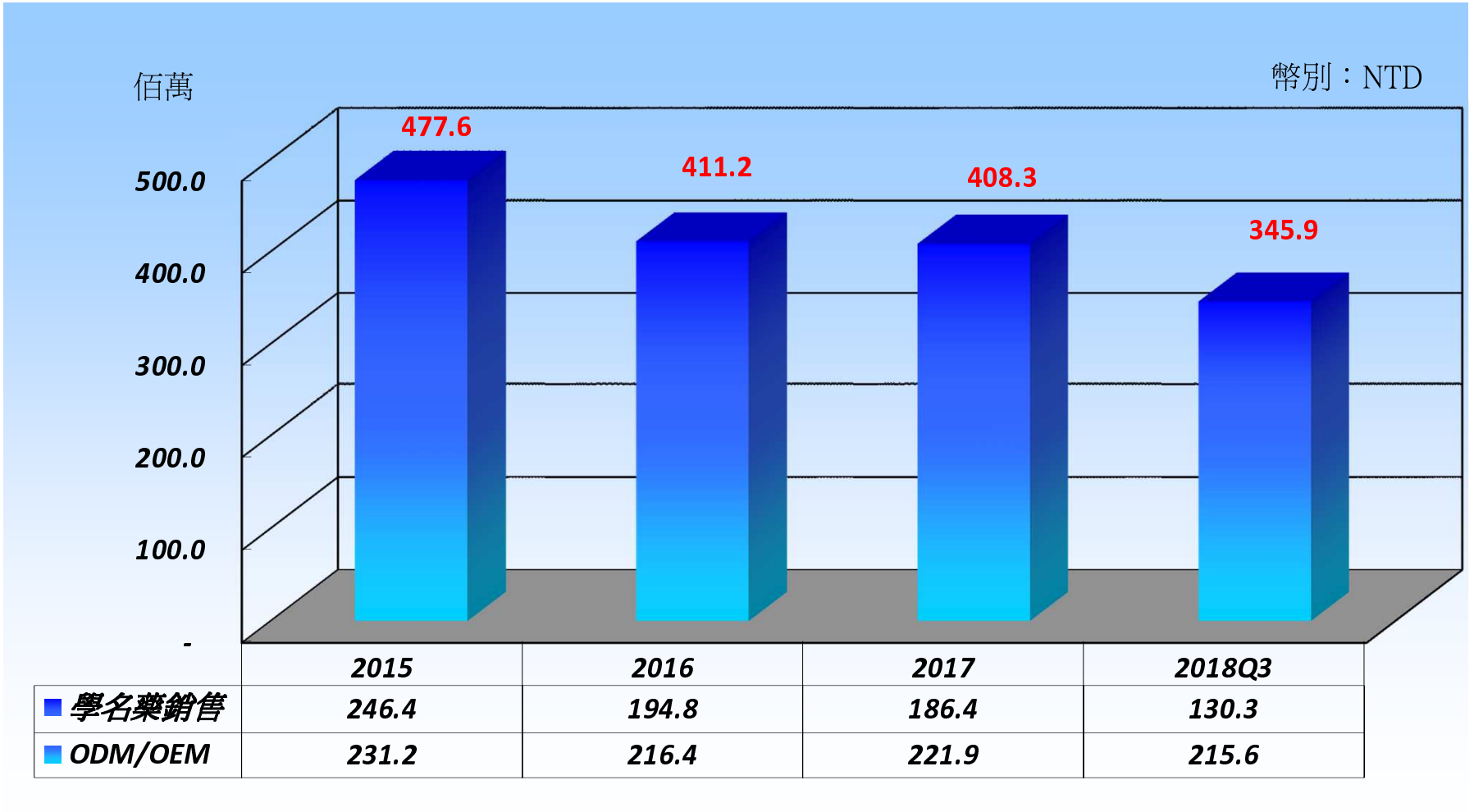
- **Planning – 2019/06**
  - IDE safety / feasibility study
  - Aricept+FUS+Sonovue
  - Aim for neurogenesis effect
  - Melbourne,AUS

- **InSightec kick-off its Phase IIa AD Clinical Study in Toronto, Nov.2018**

Stanford 完成裝機展開合作(2018/12/03)

- 機器完成安裝測試並已進行訓練課程
- 即將於本周接續進行小動物測試、並積極規劃後續臨床試驗合作所需之大動物測試
- Stanford 提議多項臨床試驗方向可供進行，內部將積極評估檢視
- 建議針對Stanford推動臨床進行、以及美國法規顧問公司積極布局

營業收入 (2015~2018 Q3)

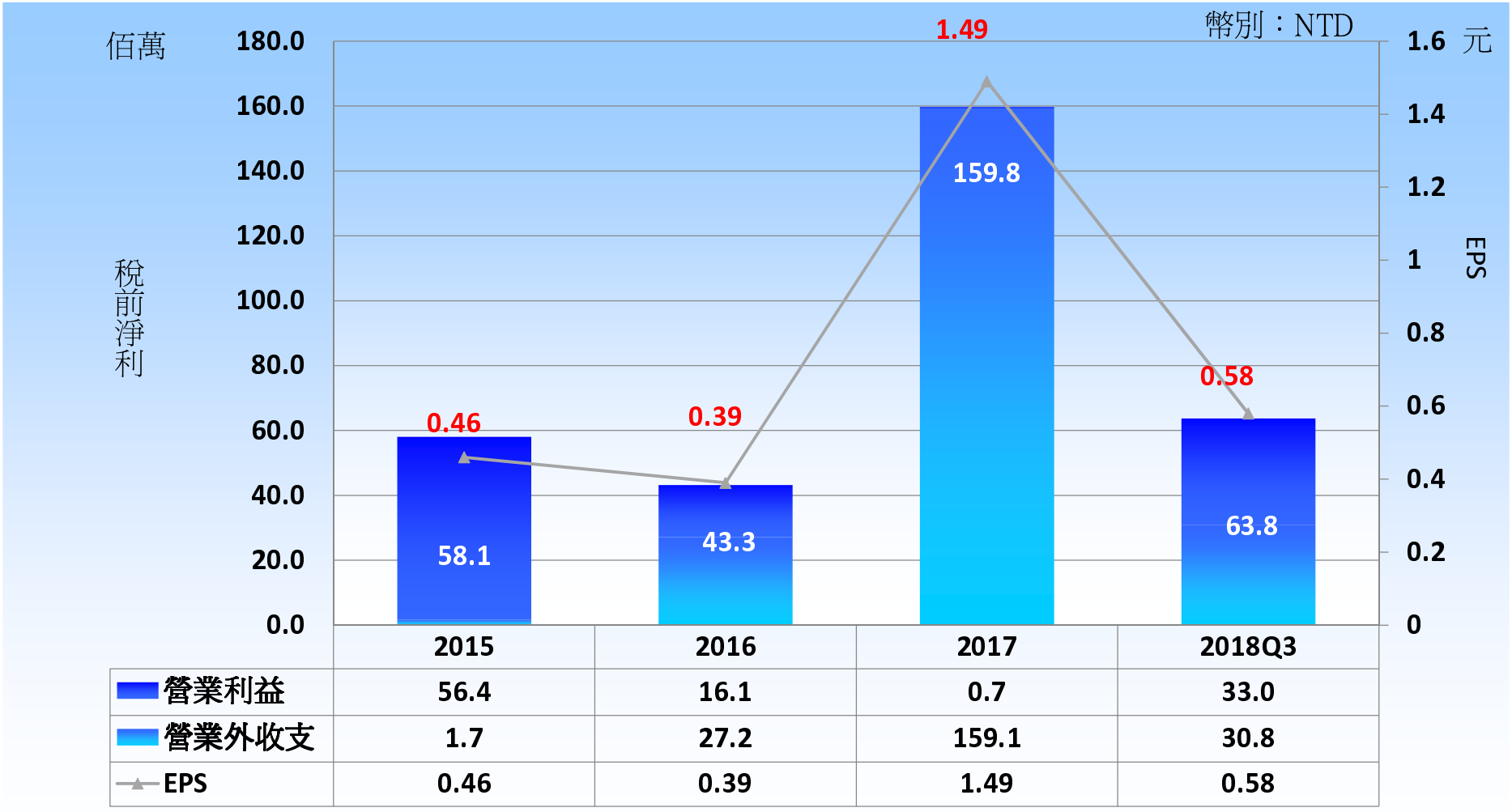


	2015	2016	2017	2018Q3
學名藥銷售	246.4	194.8	186.4	130.3
ODM/OEM	231.2	216.4	221.9	215.6

資料來源：公開資訊觀測站/合併營收

Genovate

稅前淨利（2015～2018 Q3）



	2015	2016	2017	2018Q3
營業利益	56.4	16.1	0.7	33.0
營業外收支	1.7	27.2	159.1	30.8
EPS	0.46	0.39	1.49	0.58

資料來源：公開資訊觀測站/合併綜合損益表

附件

首頁　工商　財經

狼瘡腎炎患者有福了 健亞新藥喜妥善開賣啦！

2018年12月06日 15:41 工商 社會報

健亞生技（4130）治療狼瘡腎炎的新適應症新藥Mycocep（喜妥善膠囊250毫克，主成分為Mycophenolate mofetil, MMF）自9月底取得新適應症核准，10月納入健保給付，12月初正式出貨，運達醫療院所，嘉惠狼瘡腎炎患者。

紅斑性狼瘡是一種慢性自體免疫疾病，其免疫系統無法正常運作，產生抗體，攻擊自身組織及器官，而腎臟是最常受影響的器官之一，早期接受適當治療始可延後進展到末期腎病。

對於狼瘡腎炎的治療，依據2012年美國風濕病醫學會發表的狼瘡腎炎治療指南建議：使用MMF（Mycocep喜妥善主要成分）搭配低劑量皮質類固醇為狼瘡腎炎誘導和維持治療之標準用藥。2013年發表於Rheumatology的香港長期研究結果顯示，誘導期和維持期皆使用MMF治療的患者，狼瘡腎炎的十年復發率最低。

健亞四年前，在中華民國風濕病醫學會與中華民國免疫學會之陳情及衛福部食藥署的建議下，投入MMF之開發，啟動本土唯一供查驗登記用之狼瘡腎炎臨床試驗。該試驗計畫統籌人、健亞總經理朱佳真表示，本試驗針對台灣狼瘡腎炎患者之維持性治療研究，其療效與安全性和國外臨床試驗結果類似，皆對狼瘡腎炎呈現良好的藥效和耐受性，與對照藥相比，有較少狼瘡腎炎復發的趨勢，且無白血球下降和肝發炎或受損的副作用。

該試驗結束後，為避免停藥造成患者狼瘡腎炎復發，健亞依試驗醫院「人體試驗管理辦法」之「恩慈條款」規範，持續免費提供受試者服用Mycocep，全體受試者只有一位選擇放棄，其餘全數參加，至今已服用Mycocep達二至三年，皆反應良好，進一步提供該藥品安全及療效性的實證。

衛福部2015年統計，紅斑性狼瘡患者約3萬人。依據流行病學報告，10年腎炎的罹患率約50%～60%。狼瘡腎炎屬利基市場，健亞投入臨床開發，取得五年行政保護期，短期內排除競爭對手，市場相對穩定。

健亞董事長陳正指出，健亞自1995年以來長期深耕紅斑性狼瘡治療領域，在早期曾與美國Genelabs合作，台美聯手完成七百多人的臨床三期試驗，台灣有六家醫學中心、超過兩百位病人參與，並獲得美國FDA的"Approvable"資格，為狼瘡新藥開發的領頭羊。為滿足患者的醫療需求，健亞繼續投入人力、物力，進行開發，如今Mycocep取得狼瘡腎炎適應症健保藥價上市，患者終於可以利用健保補助，減輕自費的經濟負擔。

(工商)

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Clinical trials were approved by CFDA following technology transfer

Cilostan CR Tab. of Korea United Pharm.Inc.(KUP, CEO Duk Young Kang) was approved for clinical trials(Phase 1 and 2) by CFDA(China Food and Drug Administration)

Cilostan CR Tab., which is one of Incrementally Modified Drug(IMD) and was released in 2013 after R&D for 5 years by KUP, shows significant improvement in patient compliance by taking once a day.

Cilostan CR Tab. consists of 2 layers immediate release layer and sustained release layer. It shows sustained plasma concentration for 24 hours through the Double Controlled-Release System, which KUP obtained patent from Korea and China.

KUP made a contract for technology transfer of Cilostan CR Tab. and Clanza CR Tab. with Jiangxi Jimin Kexin Pharmaceutical (JJK) in June, 2013. The value of the contract is US$69million.

JJK and KUP started licensing procedure of Clanza CR Tab. and Cilostan CR Tab. with CFDA. They passed verification test for pharmaceutical product and obtained approval for clinical trials from CFDA. JJK will conduct clinical trials(Phase 1 and 2) for Cilostan CR Tab. in China and it will take approximately 2 years. According to CFDA's regulations, final licensing will be done once the clinical trials are successful.

KUP was awarded for Technology of Developing New Drug (Cilostan CR Tab.) at the 16th Korea New Drug Award ceremony in Feb., 2015. By recording over 10 billion (KRW) sales for Cilostan CR Tab. in 2015, Cilostan CR Tab. is regarded as the 1st blockbuster product of KUP.

Korea United Pharm to up IMD sales to 50% of its total sales by 2018, says CEO

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이미지 확대

South Korean drug maker Korea United Pharm Inc. aims to increase sales of incrementally modified drugs (IMD) to around 50 percent in its entire sales by next year, said Kang Duk-young, founder and chief executive officer of Korea United Pharm.

The modified drugs market is more "sustainable" than the generic drug market that is already too crowded by many competitors, said Kang in an interview with Maeil Business Newspaper on Wednesday. He expected the company would be able to achieve the goal to raise the sales of modified drugs in its entire sales to 50 percent by next year. The revenue from modified drugs has jumped to 25 percent against its total revenue of 176.9 billion won ($155 million) last year from 4 percent four years ago.

The pharmaceutical firm has three IMDs in its pipeline this year. Last month, it released modified Cilostan CR, an antithrombotic drug that contains 200mg of cliostazol per tablet, by cutting the amount of cliostazol in half. It also plans to release modified versions of its bronchitis and antithrombotic medications in June and the fourth quarter, respectively, this year.

Kang believes that focusing on IMDs is the only way to maintain the competitiveness in the global pharmaceutical market. "We have to export IMDs rather than generics in order to compete with more affordable products supplied from China or India," he said. "We are exporting our drugs to 40 countries, but the number is not important. Maintaining sustainability is more important."

The company signed a license-out deal worth 74.3 billion won for its Cilostan CR with a Chinese drug maker last year and plans to complete a negotiation on clinical trials this

year. The Phase 1 clinical study for the Clanza CR, an anti-inflammatory drug, in China is also expected to be completed within this year.

Kang said the company also aims to increase the number of IMDs to 30 over the next five years. It has released six IMDs in the market so far, and is currently conducting clinical studies on 26 products. It has spent about 13 percent of its revenue on research and development, with last year's R&D investment reaching 13.3 percent.

The company also plans to broaden its business beyond China and South East Asia to the Middle East, Africa and Latin America. "Our operation in Vietnam is very stable, and the products manufactured in the country are shipped to many Asian countries," said Kang. The company set up retail subsidiaries in Indonesia and Thailand this year. Its Clanza CR released in 2010 has been registered in Vietnam, the Philippines and Myanmar, and exported to four countries including Russia and Ukraine.

The drug maker also plans to export its smart factory. "We plan to export automated factories on a turnkey basis in which we are responsible for every construction process along with machines, patents and technologies as a package deal," said Kang. He added there are some companies from the Middle East and Africa who have shown interest in building a smart factory with the company's aid.

Shares of Korea United Pharm closed Thursday at 20,350 won, up 2.26 percent or 450 won from the previous session.