BIOPLUS INTERPHEX KOREA

Developing a Novel Concept Regenerative Treatment for DPN:

Engensis (VM202) Phase 3 Results and Future Plans

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HELIXMITH

Disclosure

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Helixmith Overview

Pioneer and global leader in **plasmid DNA based gene therapy development** conducting multiple **late-stage clinical trials**, with a particular emphasis on diseases associated with neurological, muscular or ischemic problems

Headquarters and R&D (Dec. 2019)
Seoul, Korea

DNA Production Facility
San Diego, CA, USA

KOSDAQ (084990)

HQ

R&D oriented

120+ employees

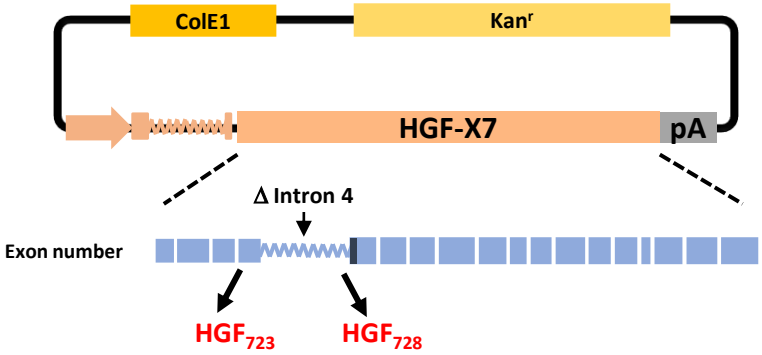
Clinical Development

Production

70+ employees

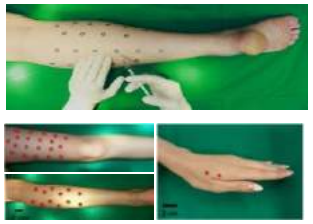
Lead Asset: Engensis(VM202)

Engensis: Plasmid DNA engineered to simultaneously express two isoforms of HGF

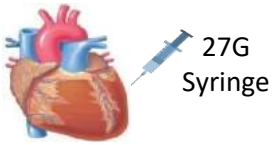


Delivery: Intramuscular injections

[Skeletal Muscle]

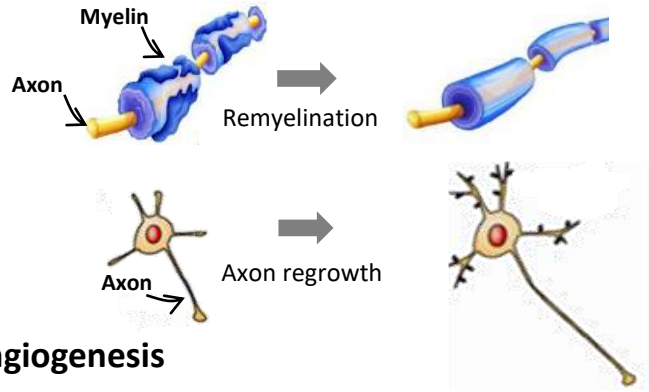


[Cardiac Muscle]

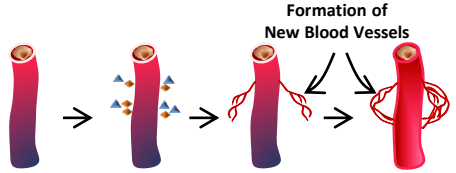


Mode of Action

1. **Regeneration of damaged nerves**



2. **Angiogenesis**

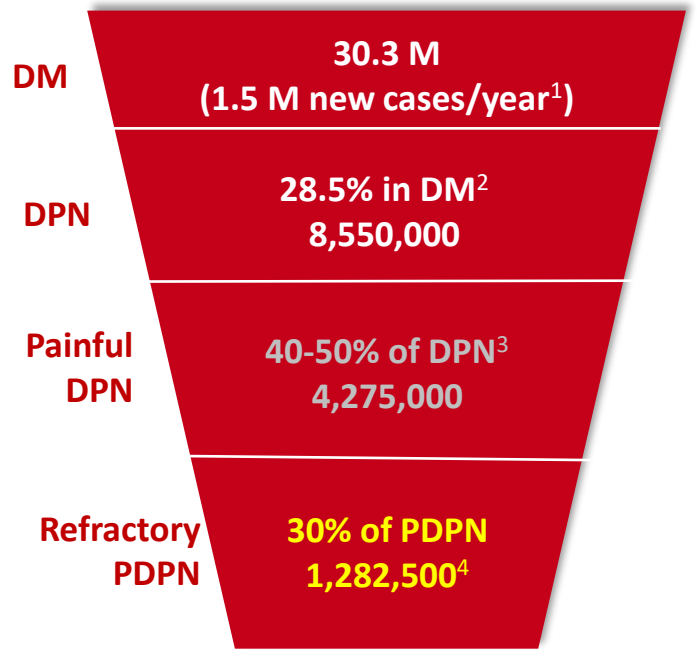


3. **Analgesic effects by controlling the expression of pain factors** (CSF-1, IL-6, α2δ1, 5-HTT, etc.)

4. **Amelioration of muscle atrophy**

Most Advanced Indication: DPN

US



Currently Used Medicines

- Anticonvulsants:
  - ✓ **Pregabalin** (Lyrica®, Pfizer) 1st Line
  - ✓ **Gabapentin** (Neurontin®, Pfizer)
- Antidepressant
  - ✓ **Duloxetine** (Cymbalta®, Eli Lilly)
- Opioid:
  - ✓ **Tapentadol** (Nucynta® ER, Depomed)
- Topical Patch:
  - ✓ **Capsaicin** (Qutenza®, Averitas)

Patients suffer from burning, tingling, throbbing, and stabbing pain

- **PDPN market size expected to grow up to $11 billion by 2026[5]**
- **US DPN market accounts for 71% among 7 MM[6]**

1 A Boulton et al. Management of diabetic peripheral neuropathy; Clinical diabetes 2005
2 MJ Young et al. A multicenter study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993 Feb;36(2):150-4
3 PDPN market research, The Dominion Group 2018,
4 PR Patil et al. Opioid use in the management of diabetic peripheral neuropathy in a large commercially insured population, Clin J Pain. 2015 May
5 Global neuropathic pain management market, Persistence market research 2018
6 PharmaPoint: Painful Diabetic Neuropathy-Global Drug Forecast and Market Analysis 2026. GlobalData, January 2018.

Key Discoveries of Phase I and II Trials

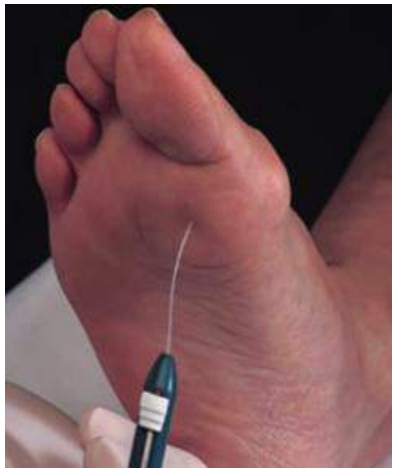
1. **VM202 has shown an excellent safety profile, especially compared to current prescription drugs**
   HGF protein levels remained relatively stable at 0.6 - 1.6 µg/ml at all time points

2. **There is an "Optimum Dose" at 16 mg per two legs per two visits.**
   One treatment is defined by the 16 mg dose which is given in two visits on two **weeks interval (Days 0 and 14), 4 mg per leg X 2 legs X 2 visits = 16 mg in total**

3. **VM202 (8 mg/leg) gave significant improvements in all pain measurements for a long period of time (Daily pain diary, BPI-DPN, VAS, PGIC)**

4. **Pain relieving effects were more pronounced in patients who are not taking Lyrica and/or Neurontin**
   (> more than 50% of PDPN populations do not or cannot use gabapentinoids.)

5. **Data from monofilament tests suggests that VM202 may aid in recovery of sensory functions and has the potential to be a regenerative or disease modifying medicine**



Engensis: Regenerative Medicine Advanced Therapy(RMAT)

**VM202 for PDPN was granted RMAT by FDA on 21 May 2018,
the first and only RMAT for a gene therapy targeting a prevalent disease**

Eligibility	• A regenerative medicine therapy in cell and gene therapy • Drugs intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition • Preliminary clinical evidence indicates potential to address unmet medical needs
Benefits	• Include all of the benefits of **Fast track** and **Breakthrough** designation programs • Allows **shorter timeline for BLA approval** including early interactions with FDA
RMAT Status	• Total 44 RMAT Designation granted[1] • Among RMAT designations for gene therapies, **only two were granted for the treatment of prevalent diseases:** ✓ VM202 (Helixmith): Diabetic Peripheral Neuropathy ✓ VY-AADC (Voyager): Parkinson's Disease

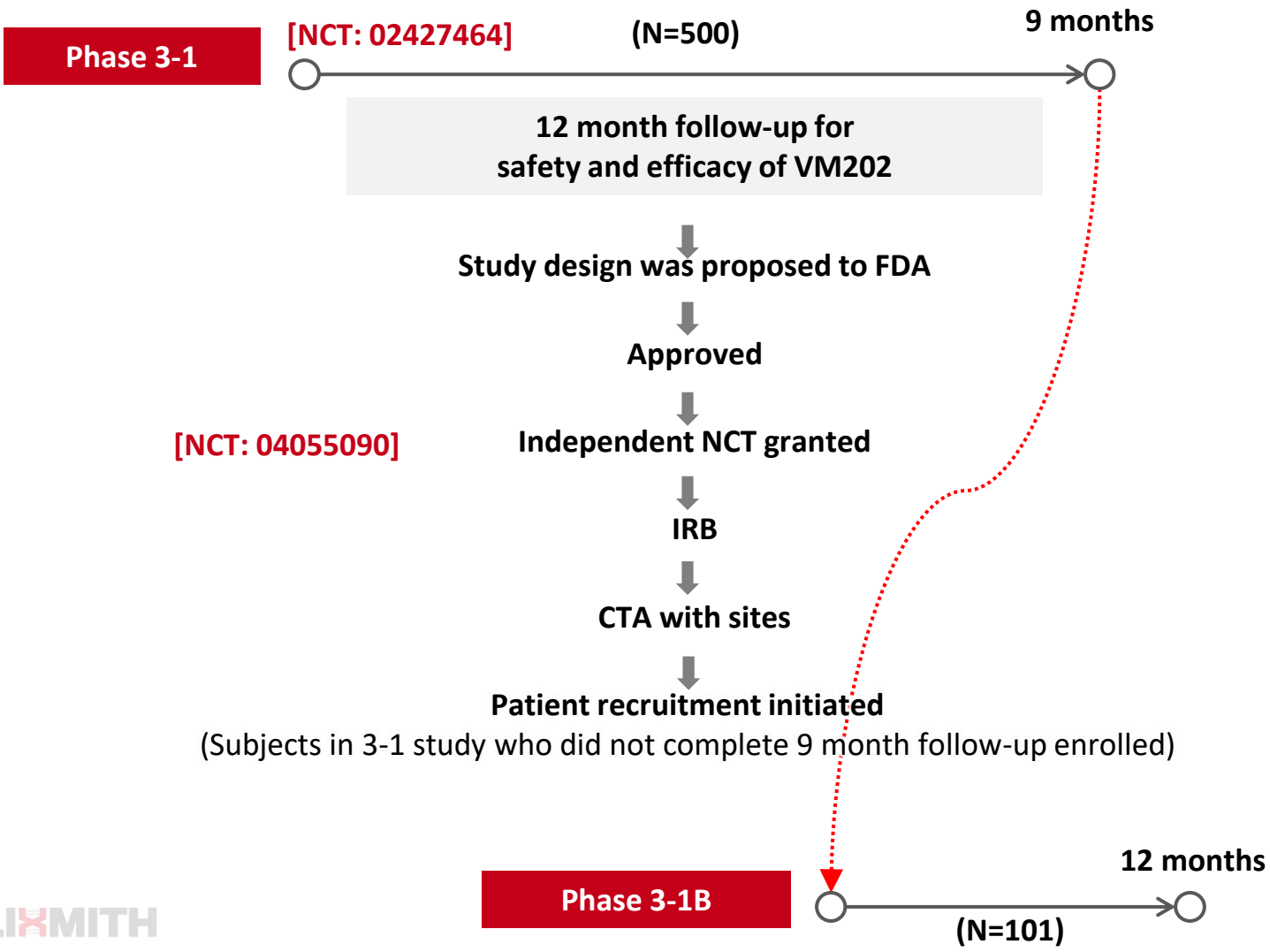
[1] Cumulative CBER Regenerative Medicine Advanced Therapy (RMAT) Designation Requests Received by Fiscal Year, FDA website, Data as of Sep, 2019

Phase 3 Study Outline

Double-Blind, Randomized, Placebo-Controlled, Multicenter Center

1. Target Indication	• Painful DPN
2. Treatment Arms	• 500 (Placebo:VM202 = 1:2)
3. Sites	• Geographically well distributed 25 sites in the US
4. Injection Scheme	• 2 treatments in 9 months • **16 mg (Days 0, 14) + 16 mg (Days 90, 104)**
5. Follow-up	• 9 months
6. Primary Endpoint	• Daily pain diary at 3 month • ≥ 50% responder at 3 month
7. Secondary Endpoint	• Daily pain diary at 6 month • ≥ 50% responder at 6 month

Phase 3 was composed of two studies, 3-1 and 3-1B



Phase 3 Results

- **When unblined, PK anomalies were observed in several subjects.**

  (Several placebo patients showed a sign of VM202 DNA in their blood samples,

  and vice versa in active group)

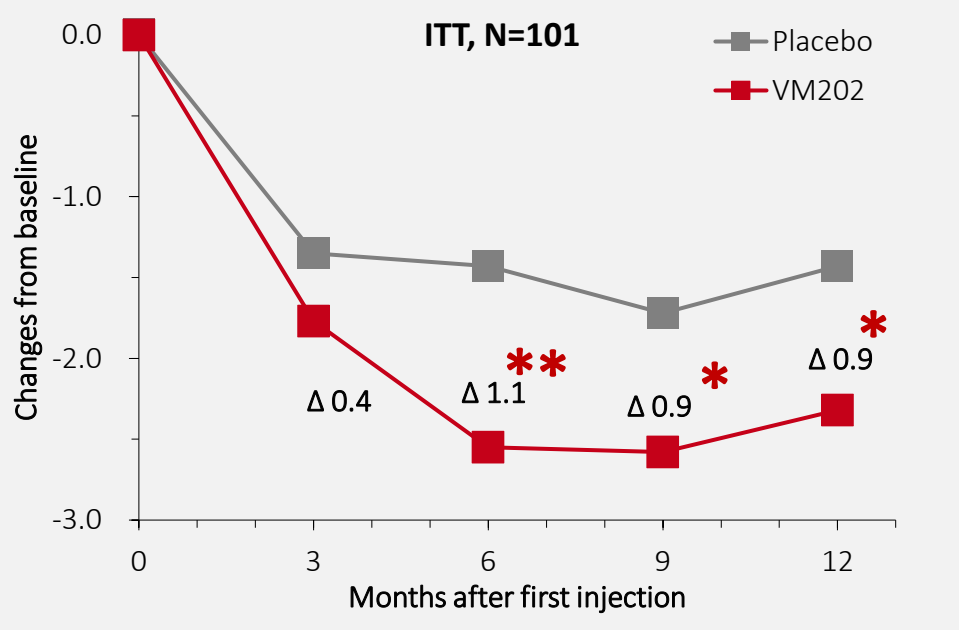
- **The 5 months investigation revealed that analytical CRO made grave mistak es in analyzing DNAs from blood samples.**

- **There was no mix-up.**

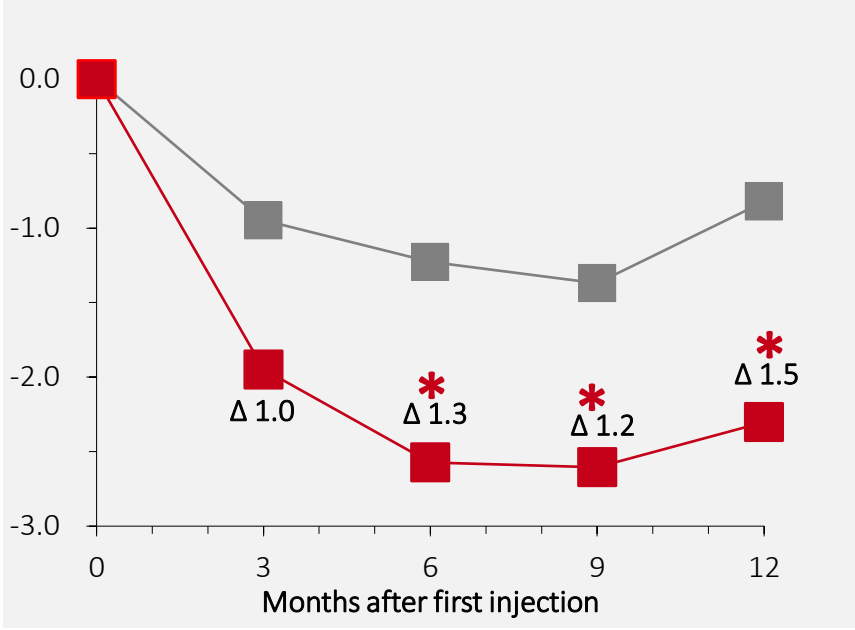
- **The 9 month 3-1 study failed to meet efficacy endpoints, while the 12 mont h study satisfied efficacy endpoints.**

Phase 3-1B Results

Mean differences (Δ) from baseline in daily pain diary scores



Effect on Pain Severity in Patients NOT ON Gabapentinoids



**p<0.05, vs. placebo group, **p<0.01, vs. placebo group*

- Statistically meaningful differences between VM202 and placebo groups for the efficacy endpoints (Month 6, 9, and 12)
- Observed efficacy sustaining up to 12 months (or nearly 9 months after last injection), suggesting the potential for disease modification
- More pronounced analgesic effect of VM202 was observed in patients not taking Gabapentinoids, consistent with phase II results

Two Factors that Have Affected Phase 3-1

PK Anomalies (PCR Aberration by CRO)

1. PCR errors

2. Label changes in:
   - Blood Samples
   - gDNA

3. (Environmental) DNA contamination

Clinical Operation Issues :

1. CRO change in the middle (~70%:~30%)

2. Higher placebo effects in the first 70%

3. Patient compliance

★ In next phase III:

- **Removal of PCR from DPN 3-2 study (and all future studies)**

  - Consistent observations of high copy numbers were already observed in many other studies.

- Plan for small, focused 7-day PK study in a small number of DPN subjects

★ In next phase III (3-2):

- Education and training of physicians and patients
- Number of sites and subjects per protocol
- 6 month follow-up
- Real-time monitoring of patients and sites
- Control of within-person pain variability

Phase 3-1B: Conclusions & Significance

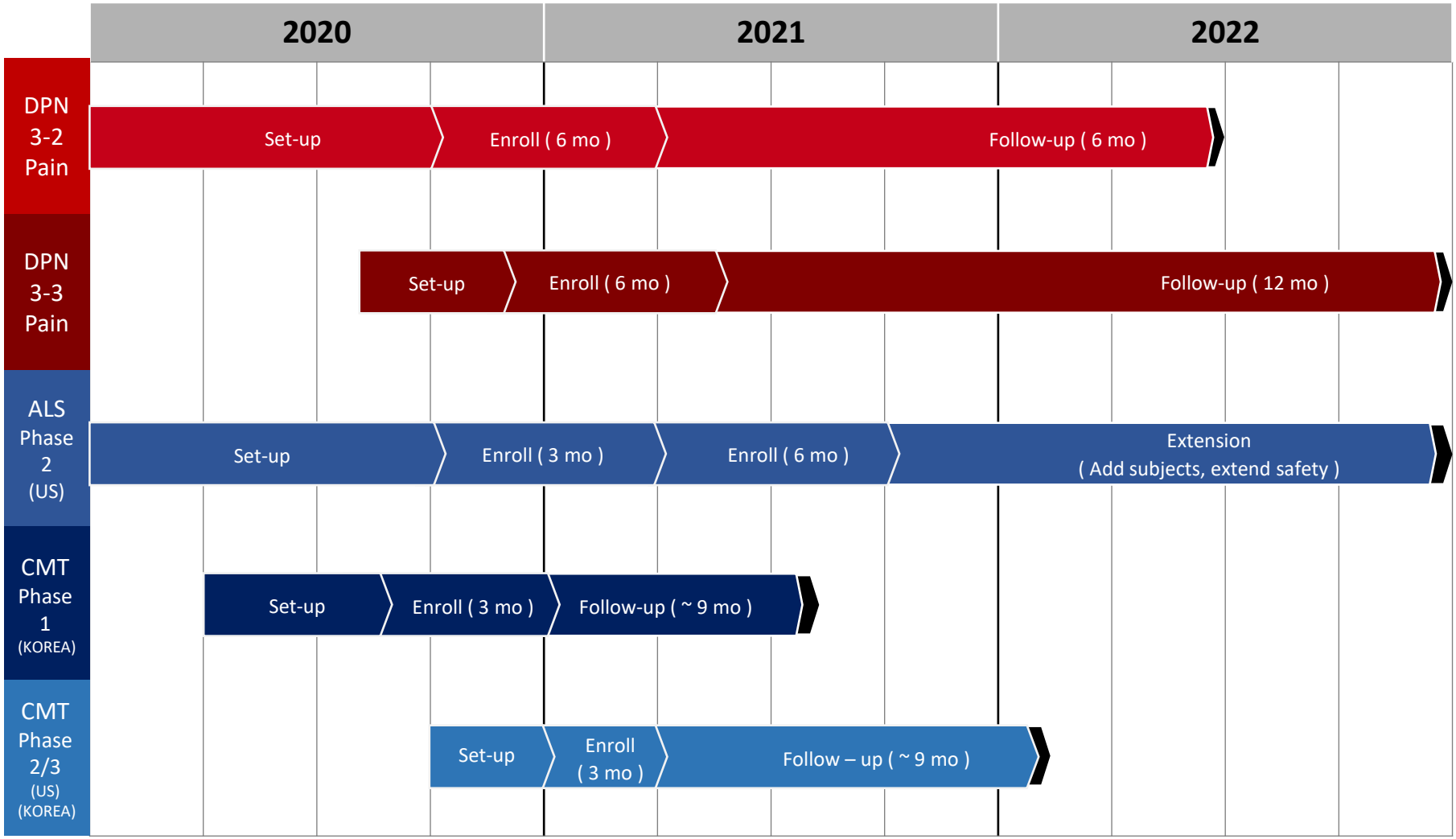
1. Excellent safety:	Little difference between placebo and VM202 groups in terms of AE with no drug related SAE observed (Number of AEs were even smaller in VM202 group.)
2. Efficacy (analgesic effect):	Δ values between VM202 and placebo were 1.1, 0.9, 0.9 at 6, 9, 12 months respectively (p=<0.05) in the ITT (N=101)
3. Efficacy in patients NOT taking gabapentin and/or pregabalin:	In the patients not taking gabapentinoids (N=53), the Δ values were even greater 1.3, 1.2, 1.5 at 6, 9, 12 months respectively (p=<0.05)
4. Regenerative Medicine Potential:	**Significant analgesic effect was observed even in the absence of VM202 DNA and HGF protein expression, for 8 months** after the last injection of VM202. This result, combined with VM202 MoA data, strongly suggests VM202 may have nerve regeneration properties, which can add significant value to the pricing of VM202

DPN Phase 3-2 Study

Short Title: Phase 3 Study to Assess Safety and Efficacy of Engensis in Painful Diabetic Peripheral Neuropathy

1. Target population	• Painful DPN, not on gabapentinoids
2. Sample size	• 152 (up to 250, adaptive), Engensis:placebo = 1:1
3. Sites	• 15 sites, US only
4. Injection scheme	• 2 treatments • 16 mg + 16 mg (Day 0/14, Day 90/104)
5. Follow-up	• 6 months
6. Primary endpoint	• Change in Average Daily Pain (ADP) score at 6 month
7. Secondary endpoint	• Safety – TEAE, SAE • Cellular and Humoral Immune response • Change in Worst Pain score at 6 month (BPI-DPN) • 50% responder rate (ADP)
8. Exploratory endpoint	• Bedside Sensory Testing – Disease Modification

Engensis(VM202) Development Roadmap



Therapeutic Platforms

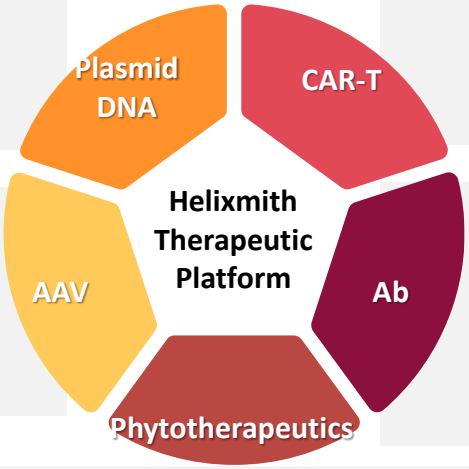
As a pioneer of gene therapy, Helixmith has been developing on the following therapeutic platforms with the promising technical know-hows, which will be a viable approach to treat human diseases.

Plasmid DNA

- Helixmith has promising technical know-hows to develop gene therapies targeting a broad range of indications

CAR-T

- Helixmith has been developing CAR-T therapies with its exclusive retroviral gene delivery platform, optimized for safety and gene expression efficiency



Adeno-associated Virus (AAV)

- Through animal studies, Helixmith discovered the most effective method for viral vector delivery – intrathecal injection

Agonistic Ab

- Helixmith is developing drugs using agonistic Ab that can activate cMet (HGF receptor), to target kidney diseases caused by various factors, a field with very high unmet medical need.

Phytotherapeutics

- Creating value by developing robust drug and promoting health by using body friendly greens

Manufacturing Facility

Helixmith has established manufacturing facility in San Diego to solve the manufacturing bottleneck in biopharma industry with accumulated experiences and know-hows in gene therapy market.

Pioneer of commercial plasmid DNA manufacturing facility

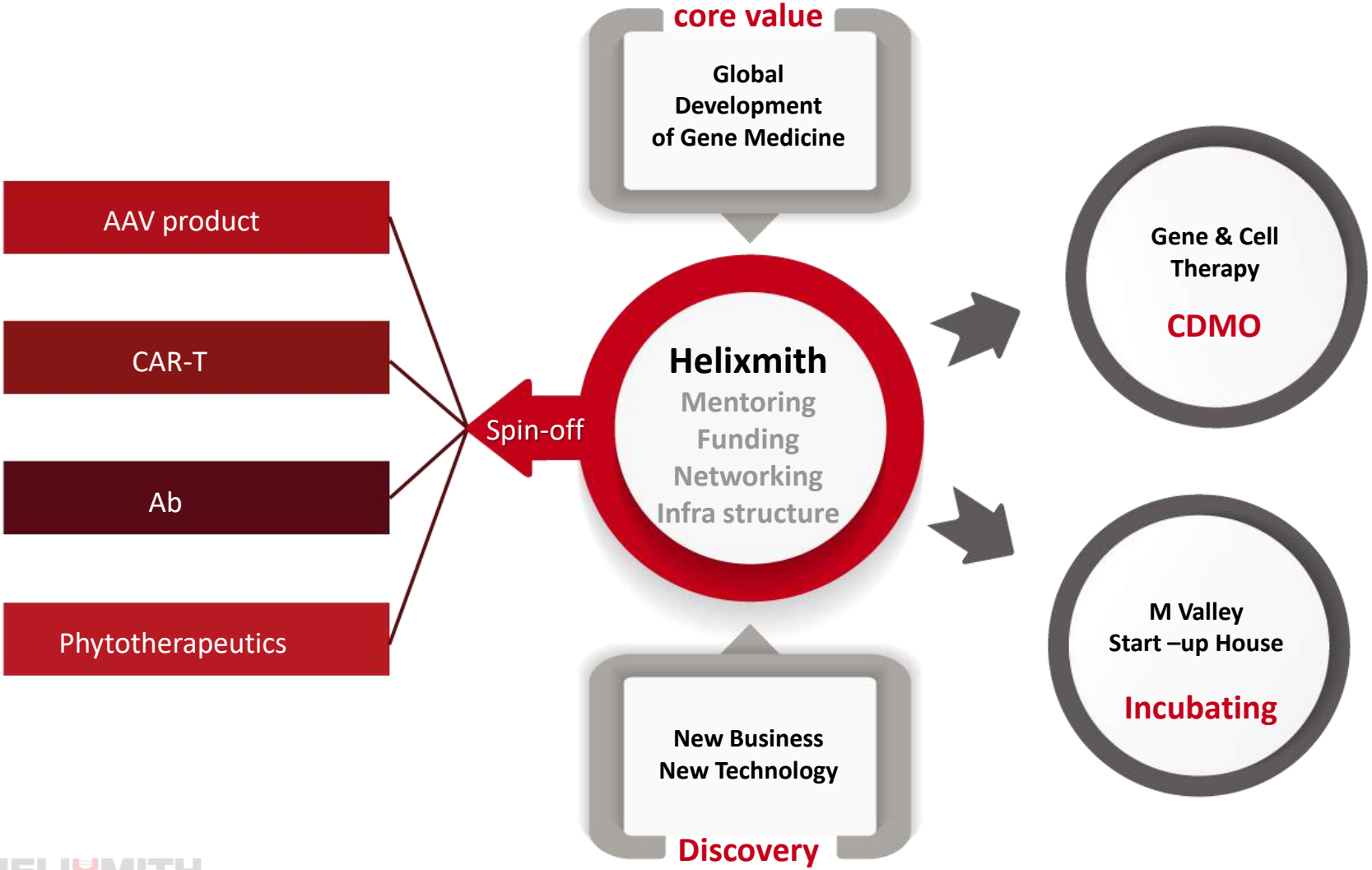
High quality and reliable in-house production capability for both clinical and commercial scale

Contract Manufacturing Organization (CMO) service for other biopharmaceutical companies

Plasmid DNA Production Facility Specification

- GMP-ready production facility with successful experience in regulatory due diligence
- 68,400 ft^2 plant
- 500 L fermenter, cell culture lab and QC test lab, etc.
- Extra space (> 174,000 ft^2)to be equipped with 60-300L and 5-50L fermenter
- 40+ employees highly experienced in large-scale production of plasmid DNA

Building R&D Ecosystem



BIOPLUS INTERPHEX KOREA

Sep. 23~25, 2020 COEX, Seoul

HL036 안구건조증 치료제 글로벌 임상 개발 전략

Clinical Development Strategies of HL036 Ophthalmic Solution for the Dry Eye Disease

HANALL BIOPHARMA 한올바이오파마 | 주 대웅제약

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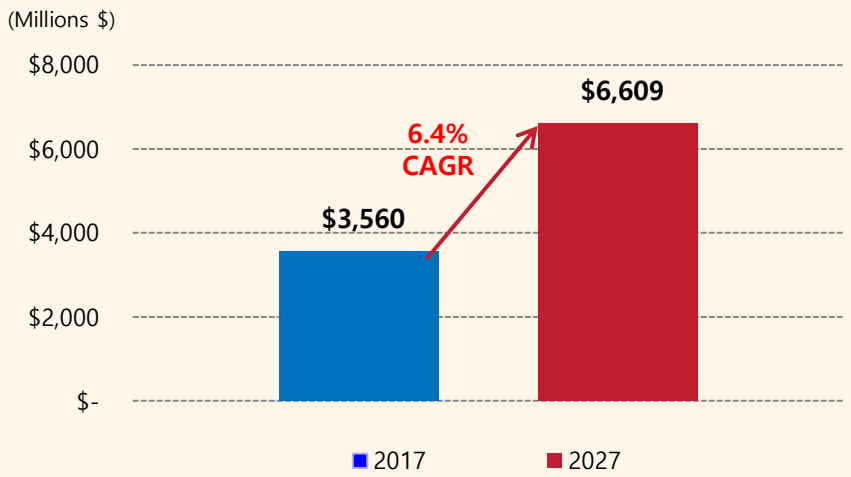
본 자료의 활용으로 인해 발생하는 손실에 대하여 당사나 당사의 대리인들은 과실이나 기타의 경우 포함하여 어떠한 책임도 부담하지 않음을 알려드립니다. 본 자료는 주식의 모집 또는 매매 및 청약을 위한 권유의 목적으로 구성되지 않았으며, 자료의 어느 부분도 관련 계약 및 약정 또는 투자 결정을 위한 기초 또는 근거가 될 수 없음을 알려드립니다.

Dry Eye Disease (DED)

- **Definition:** "**Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms,** in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." (DEWS II (2017))
- **Prevalence:** 인구의 5~6%가 영향 받고, 0.4~0.5%가 DED로 진단됨, 폐경기 이후 여성 유병률은 7.8%
- **원인:** 노화, 여성호르몬 감소, 관절염이나 쇼그렌 증후군과 같은 동반 질환, 부교감신경 차단제, 항히스타민제, 베타차단제, 수면제, 피임약 등과 같은 약물복용, 갑상선 질환, 만성결막염, 환경적 요인 등

http://www.sarahknowseyes.com/

Global market for dry eye disease treatment



(Source : Future Market Insights 2017)

- **전세계 시장 중 북미시장이 $2.5 Bn**에 달해 **70%를 차지**하고 있으며 **시장성장률**도 **연평균 6.7%로 예상**
- **FDA허가 안구건조증 치료제**
  - **Restasis (Allergan)** - Sales: $1.3 billion (2018)
  - **Xiidra (Shire)** - '16년 허가, $388 million (2018)

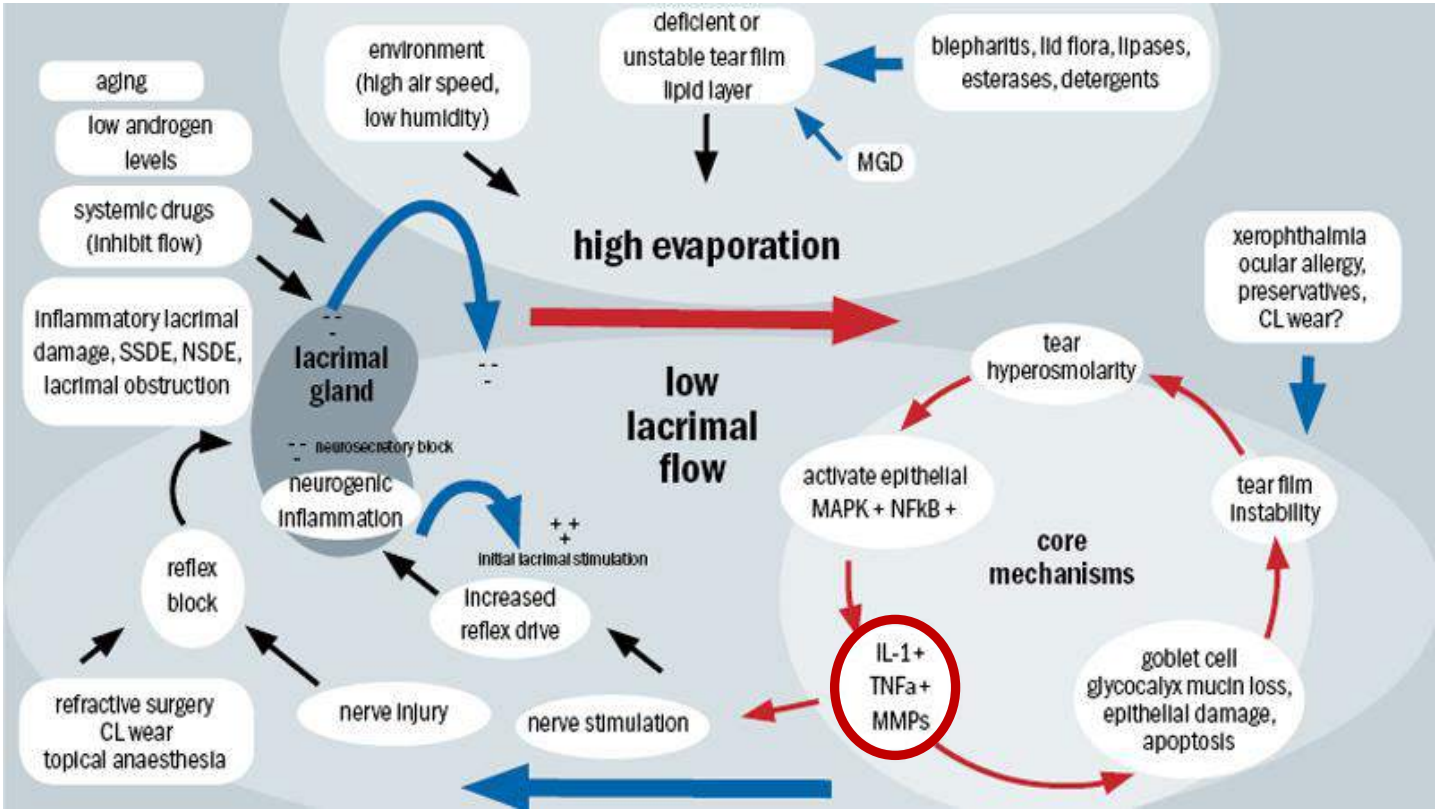
→ 미국 FDA에서 승인된 안구건조증 치료제는 단 3개뿐이며, 치료효과가 만족스럽지 못한 상황

→ **약효가 개선된 새로운 치료제에 대한 needs 높음**

Main Mechanisms of Dry Eye Disease (DED)

The Vicious Cycle of DED

① High evaporation or Low lacrimal flow
② Tear hyperosmolarity
③ Activation of epithelial MAPK/NFκB
④ Proinflammatory cytokines (IL-1, IL-6, TNF)
⑤ Epithelial damage and apoptosis → mucin loss
⑥ Tear film instability



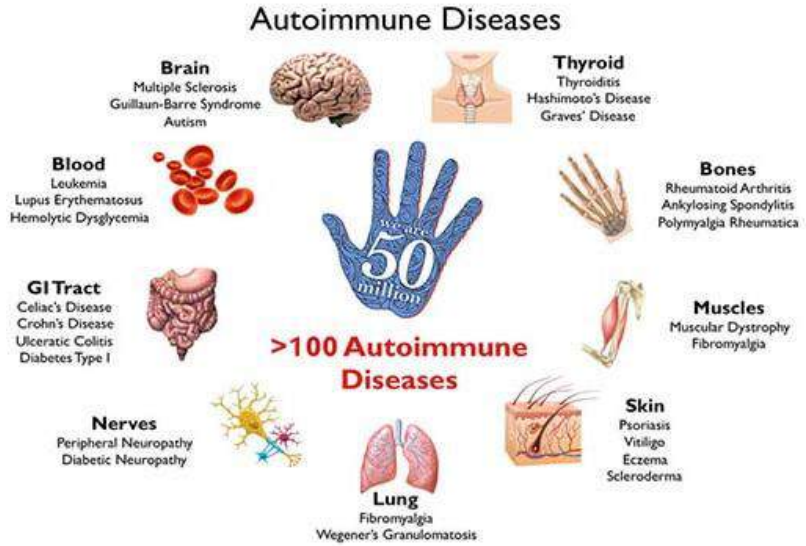
Optician (2017) https://www.opticianonline.net/

Tanfanercept, A Designed Anti-TNF Molecule for Topical Use

- **Tanfanercept : 국소투여에 최적화된 Anti-TNF 단백질**

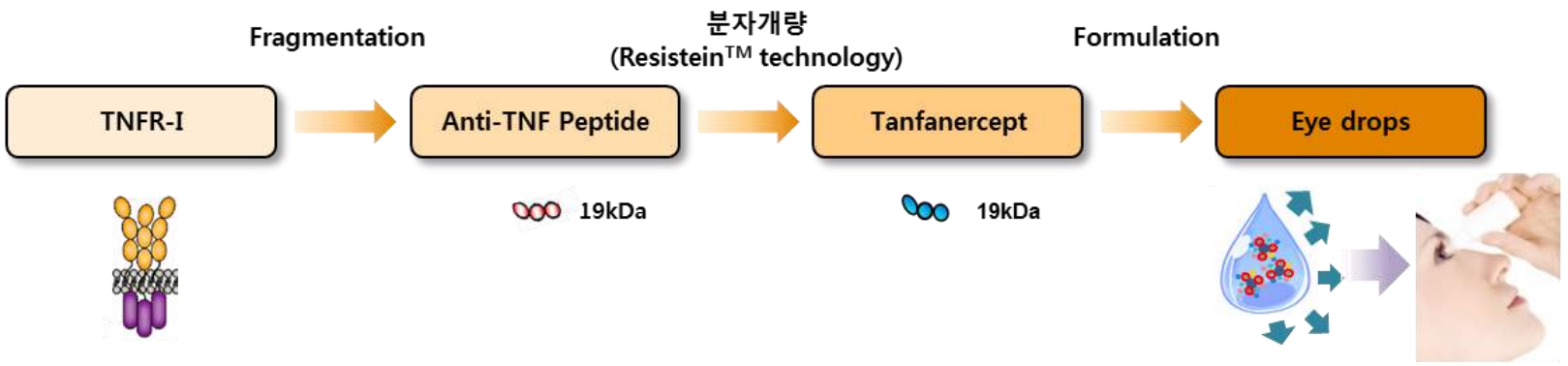
✓ 크기 축소로 분자밀도 8배 증가
✓ TNF 중화능력 260배 증가
✓ 탁월한 조직분포/잔류 능력
✓ 대장균을 이용한 저가 생산

→ 염증성 안구질환용 점안액
- 안구건조증
- 비감염성 포도막염



https://microbenotes.com/autoimmune-disease/

HL036 분자개량 및 제제화 과정



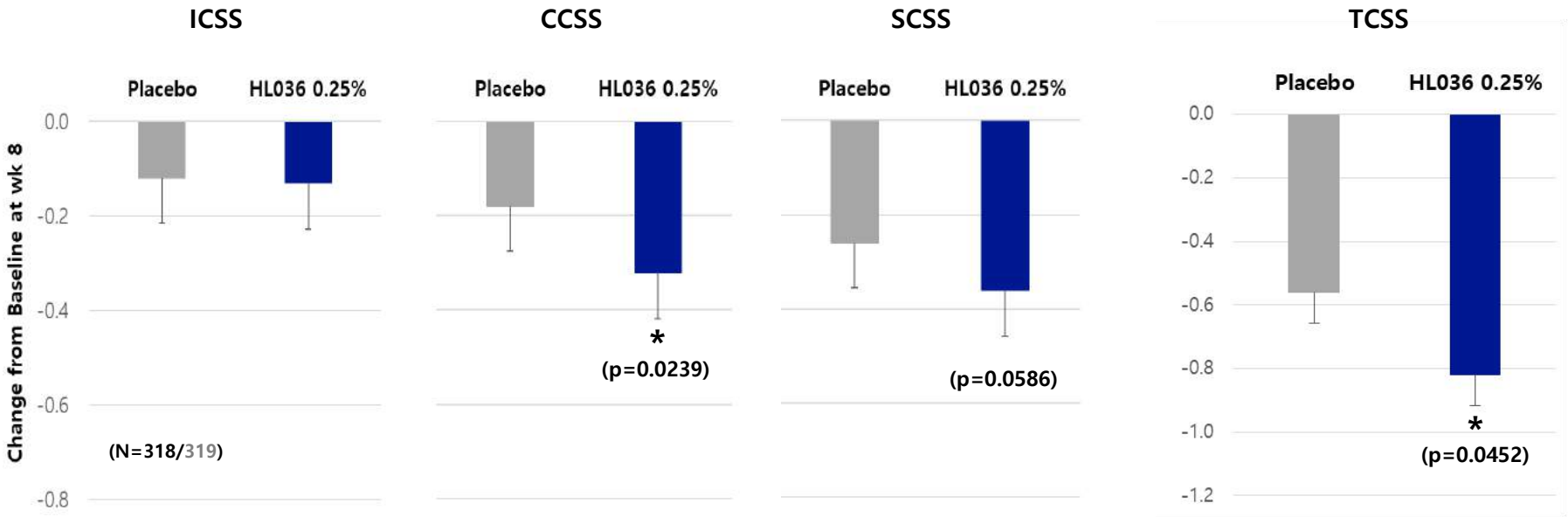
Clinical Development of HL036 Ophthalmic Solution for DED

	-	VELOS-1	VELOS-2	VELOS-3*	VELOS-4*
Stage	**Phase 1**	**Phase 2**	**Phase 3-1**	**Phase 3-2**	**Phase 3-3**
Purpose	Safety and Tolerability	Efficacy in Sign & Symptom	Efficacy in Sign & Symptom	Efficacy in **Sign**	Efficacy in **Symptom**
Country	South Korea	US	US	US	
Timeline	Completed in 2016	Completed in 2018	Completed in 2020	Planning to **initiate in 2021**	
Subjects	Healthy volunteers	Mild-to-Moderate Sign & Symptom Patients	Mild-to-Moderate Sign & Symptom Patients	**Moderate-to-Severe Sign** Patients	**Moderate-to-Severe Symptom** Patients
Groups	HL036 0.05%, n=8 HL036 0.5%, n=8 Placebo, n=4	HL036 0.1%, n=50 HL036 0.25%, n=50 Placebo, n=50	HL036 0.25%, n=318 Placebo, n=319	HL036 0.25%, n=XX Placebo, n=XX	HL036 0.25%, n=XX Placebo, n=XX
Treatment	BID for a day	BID for 2-week Screening and 8-week Treatment		Same as left	
Primary Endpoints	Ocular examinations, Systemic examinations	ΔICSS for sign ΔODS for symptom	ΔICSS, CAE for sign ΔODS for symptom	**ΔCCSS for sign** ΔEDS for symptom	**ΔEDS for symptom** ΔCCSS for sign
Secondary Endpoints	HL036 PK in serum	ΔCCSS, ΔSCSS, ΔTCSS, Conjunctival redness, Schirmer's test, TFBUT, ΔEDS, ΔOSDI, ΔOD&4S	ΔICSS, ΔCCSS, ΔSCSS, ΔTCSS, Conjunctival redness, Schirmer's test, TFBUT, ΔEDS, ΔOSDI, OD&4S	ΔICSS, ΔSCSS, ΔTCSS, Conjunctival redness, Schirmer's test, TFBUT, ΔODS, ΔOSDI, OD&4S	

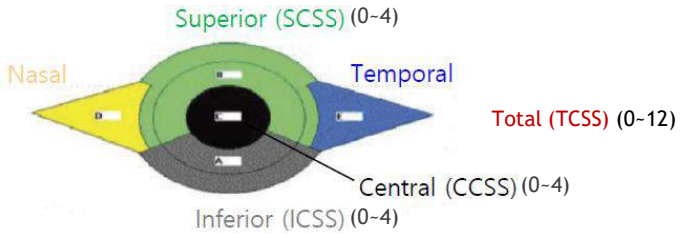
* Tentative plan

Sign Improvement observed in VELOS-2 Study

➢ **Change of Corneal Staining Score (CSS) from Baseline at Week 8**

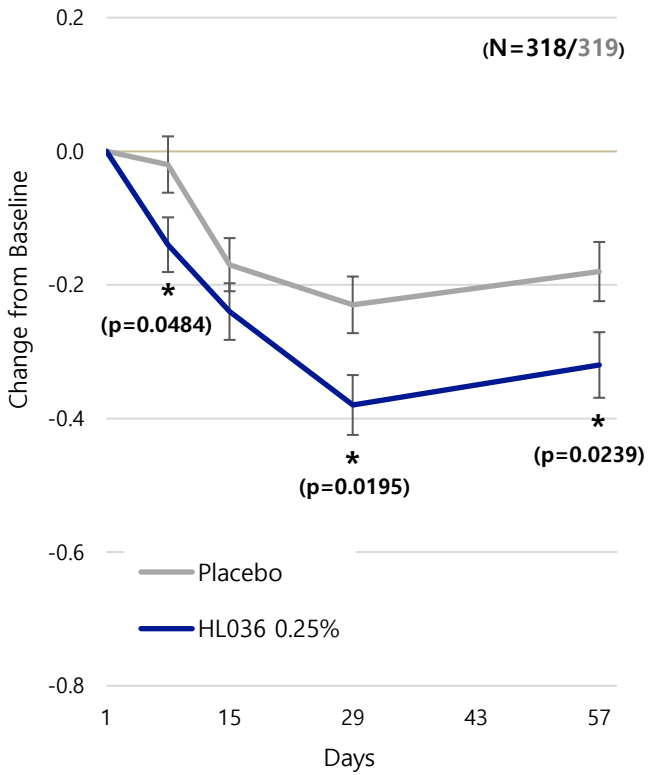


Ora Calibra® Corneal Staining Score (CSS)

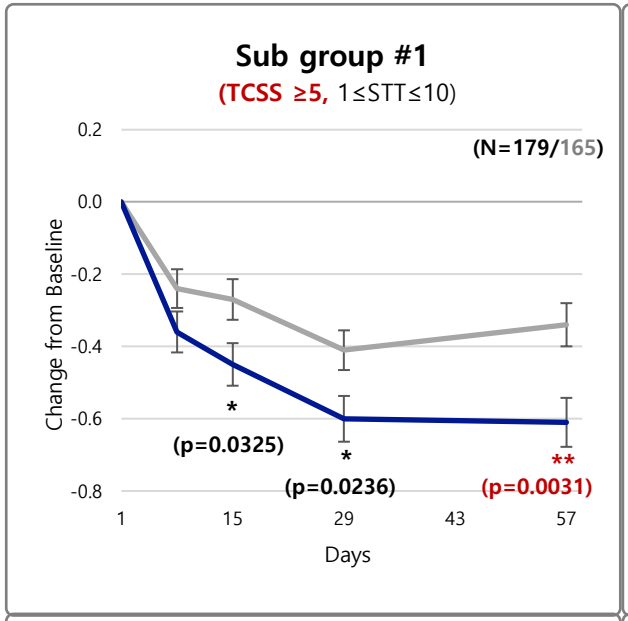


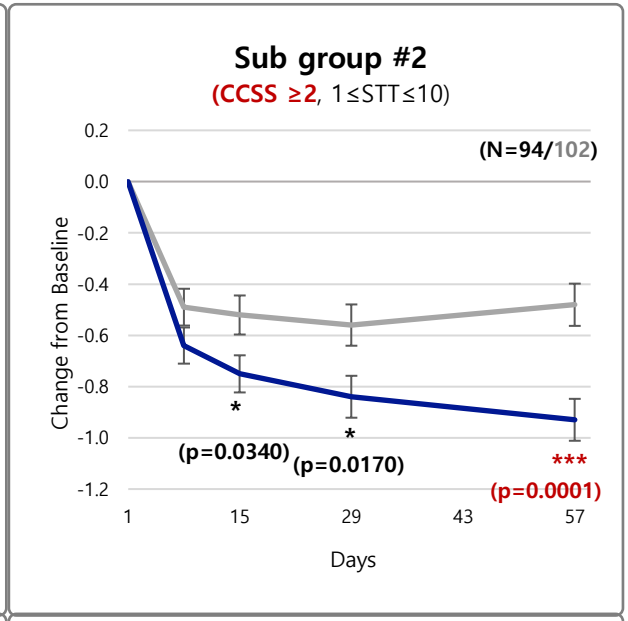
0	None	no staining
1	Trace	occasional
2	Mild	countable
3	Moderate	uncountable, but not confluent
4	Severe	confluent

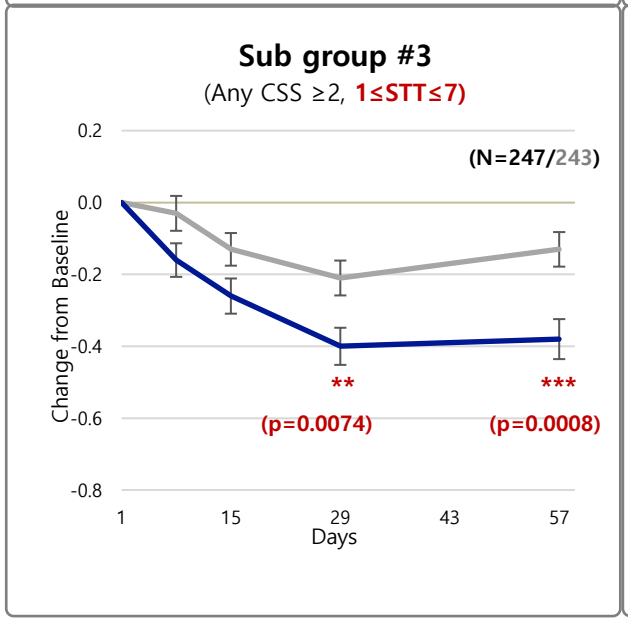
Subgroup Analysis in CCSS according to Baseline Severity

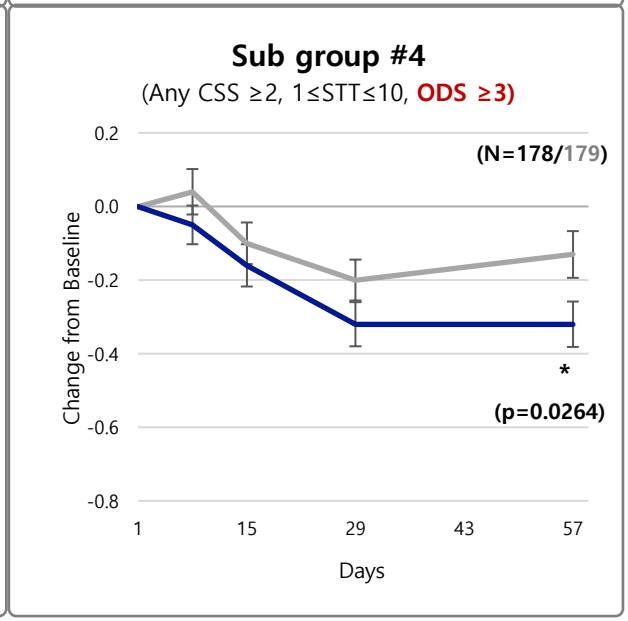


*Any CSS: CSS at least one region









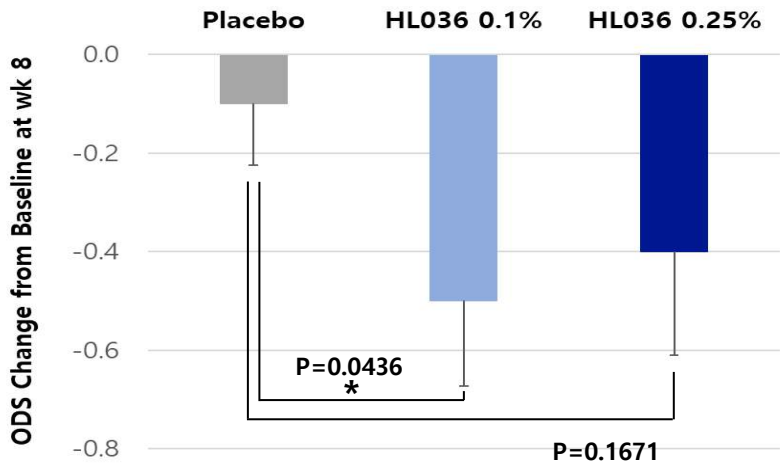
p-value by two-sided t-test; * , p<0.05; ** , p<0.01; ***, p<0.001

Symptom Improvement observed in VELOS-1 and VELOS-2 Study

임상2상 (VELOS-1 Study)

(N=50/50/50)

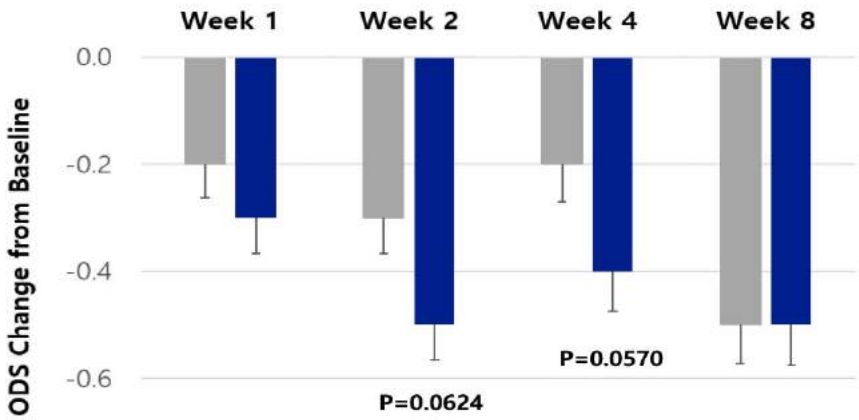
Ocular Discomfort Score (ODS) at week 8



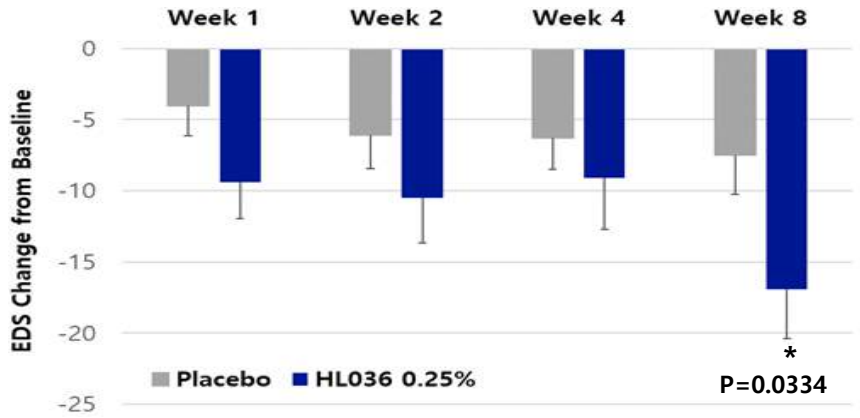
임상3상 (VELOS-2 Study)

(N=319/318)

Ocular Discomfort Score (ODS), ITT



Eye Dryness Score (EDS), Subgroup



What we learned from VELOS-1 and VELOS-2 Study

HANALL BIOPHARMA 한올바이오파마 | 주

Dry Eye Disease

- **Heterogeneous patient populations:**
  - different pathologies mixed (aqueous deficiency vs. high evaporative)
- **Lack of correlation of signs and symptoms**
- **Control interventions** having a strong placebo effects

Tanfanercept

- **Fast and sustained sign improvement in central cornea**
- **More treatment effects on more severe patients**
- **Favorable drop comfort score** comparable to artificial tear

Clinical Operational Challenge

- The devil is in the detail (**art of CRO management**)
- Pros and cons of using **various diagnostics and monitoring tests**
- Study design/methodology **tailored to Tanfanercept and its MOA**

Future Clinical Development Strategy

- **Separate studies** of respective sign and symptom primary end point
- **Central corneal staining score (CCSS)** as our primary sign end point
- **More sensitive symptom measure** as primary symptom end point
- **Enriched patient populations with more treatment sensitive group**
  - More inflammatory pathology (less placebo effect)
  - Moderate-to-Severe baseline sign and symptoms
- Developing together **with key global experts**

Next Clinical Development Plan (Tentative)

	-	VELOS-1	VELOS-2	VELOS-3*	VELOS-4*
Stage	**Phase 1**	**Phase 2**	**Phase 3-1**	**Phase 3-2**	**Phase 3-3**
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* Tentative plan

HANALL BIOPHARMA 한올바이오파마 | 주

BIOPLUS INTERPHEX KOREA

Clinical Development of Olinvacimab

Jin-San Yoo

CEO, PharmAbcine

CONTENTS

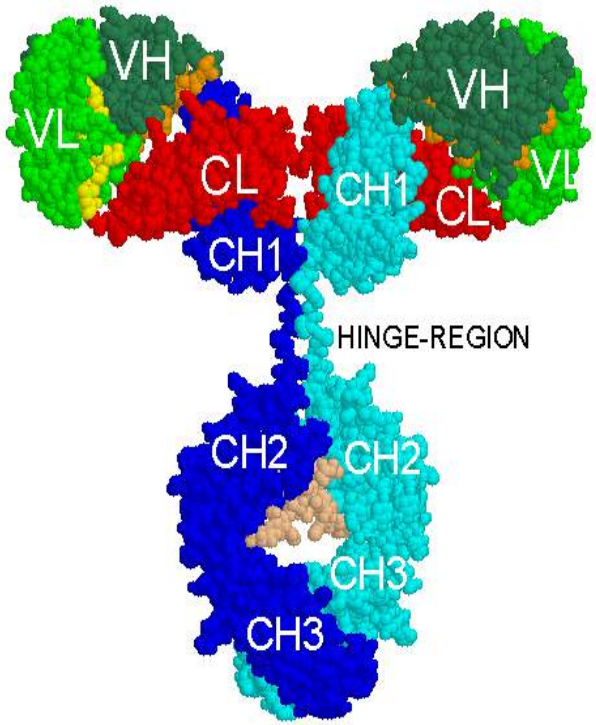
Olinvacimab(TTAC-0001) - hVEGFR-2 Neutralizing, Fully Human Antibody

Target: VEGFR2 (KDR)

Fully human lgG1

Kd: 2.3X10^{-10} M

Non-internalizing antibody



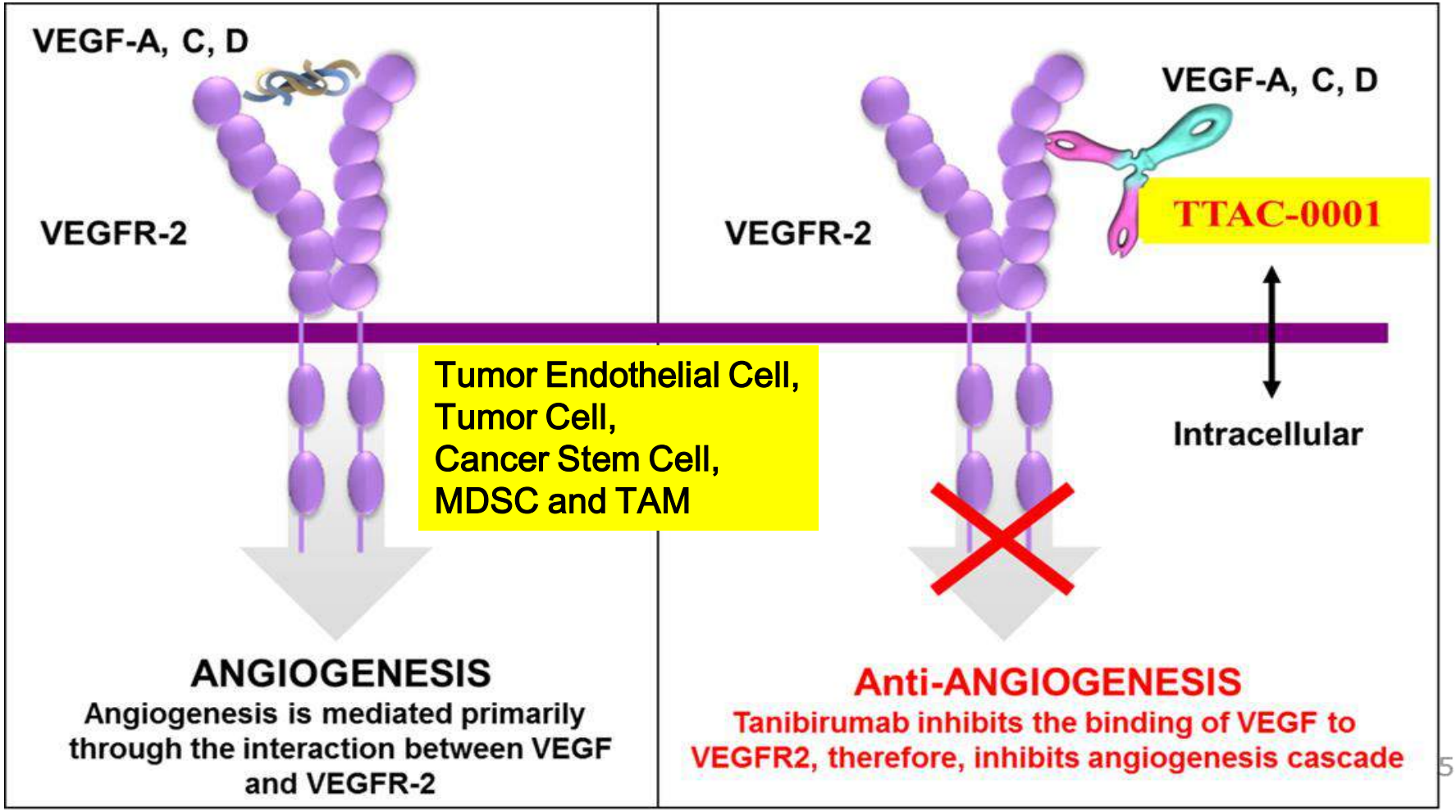
- Human/Mpise/Rat/Cyno
- Cross-Species reactivity

Binding on CML cell line (K562) & leukemic cell line (HL-60)

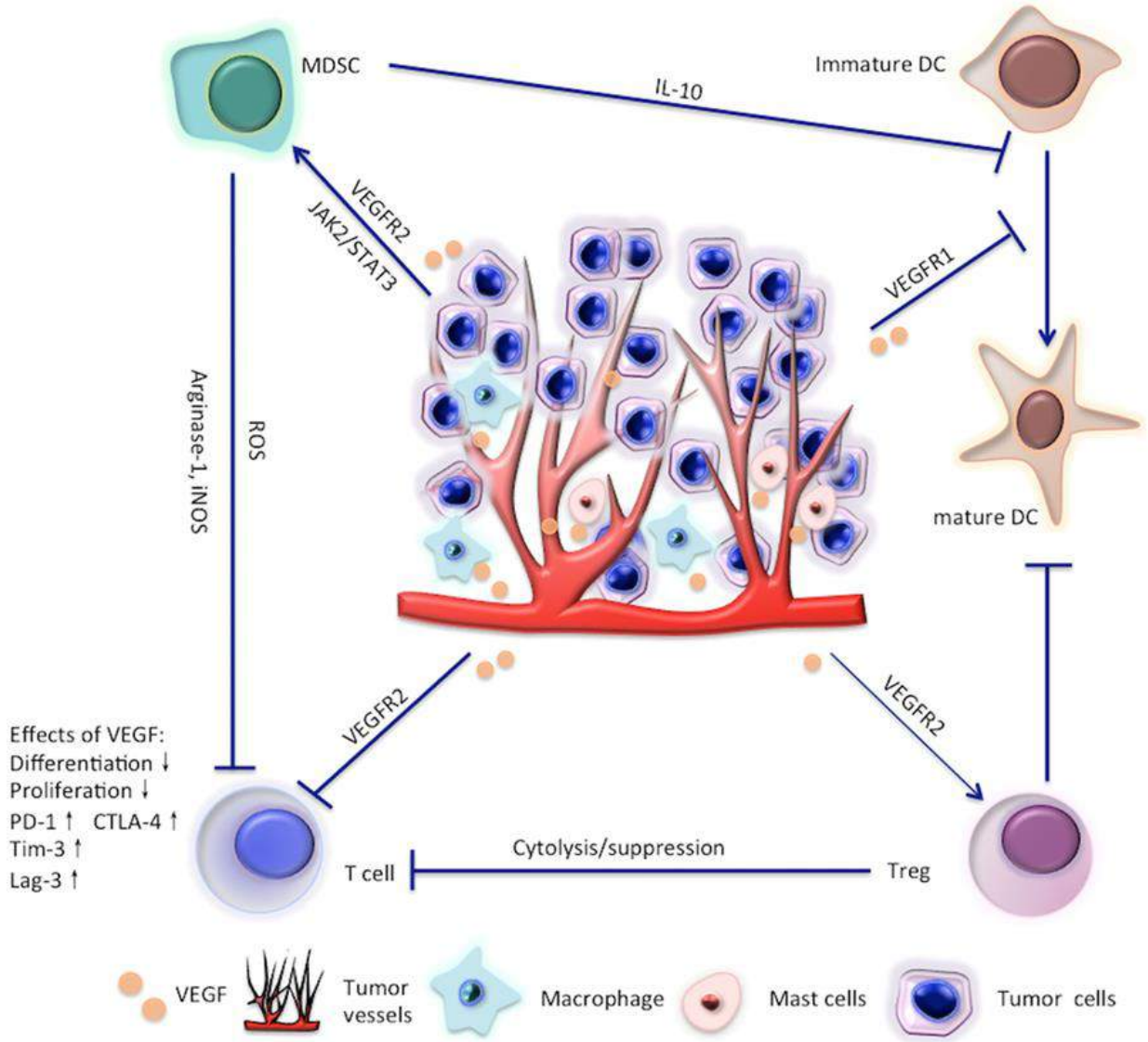
Anti-cancer activity : Colon, breast, lung, Glioblastoma, liver, etc

No normal human tissues cross reactivity

Olinvacimab neutralizes both auto- and paracrine VEGF-VEGFR2 pathways & downstream effector function, leading to apoptosis/necrosis



Olinvacimab plays pivotal role in both tumor angiogenesis and immune modulator of TME



https://www.frontiersin.org/articles/10.3389/fimmu.2018.00978/full

Phase I Trial
at Samsung Medical Center, S. Korea

PI: Young Suk Park

Patients: All comers except GBM or rGBM patients for DLT determining study

http://www.samsunghospital.com/m/reservation/common/doctorProfile.do?DR_NO=313

Olinvacimab Phase I summary

- Up to cohorts 8 (24 mg/kg) has no DLT(Dose Limiting Toxicity) observed.
- Study of PK/PD from Phase I suggested that increase of some biomarkers (VEGF-A, sVEGFR-2, PlGF) were observed.
- Displayed no common severe side effects like hypertension, bleeding, hemorrhage, gastric/lung perforation or proteinuria appeared in Cyramza, Avastin, Zaltrap, Sutent, Nexavar and other VEGF antagonists.
- Shown several SD patients (61%) from all terminal stage cancer patients in Phase I.
- Revealed grade 1 or 2 reversible capillary hemangioma on the skin to 50% of patients who were treated with Olinvacimab

PharmAbcine

Antibody Therapeutics for Life

goes to

Olinvacimab phase 2a with recurrent GBM trial

Olivia Newton-John Cancer Research Institute

Sir Charles Gairdner Hospital

Olinvacimab PhIIa rGBM Clinical Trial Data Presented:

Phase IIa recurrent GBM Clinical Trial summary

Overall response rate (ORR, rate of subjects showed CR or PR) was not observed from 12 subjects. Meanwhile, **disease control rate (DCR, including stable disease) showed from 3 among 12 subjects (25%)**

Subject 1102 – stayed in the trial for **13 cycles** (about 1 year) permitted by protocol and treated for 3 cycles more with special access program allowed by governance. This patient had stable disease during study period and tumor related problem such as gait disturbance or visual field defect were not aggravated so had satisfactory result aspect of quality of life.

Subject 2202 – target tumor size was **reduced up to 80%** from baseline but completed as PD due to new lesion. She was treated with Avastin for 6 months after stop of TTAC-0001 without disease progression. More than 1 year of survival was reported.

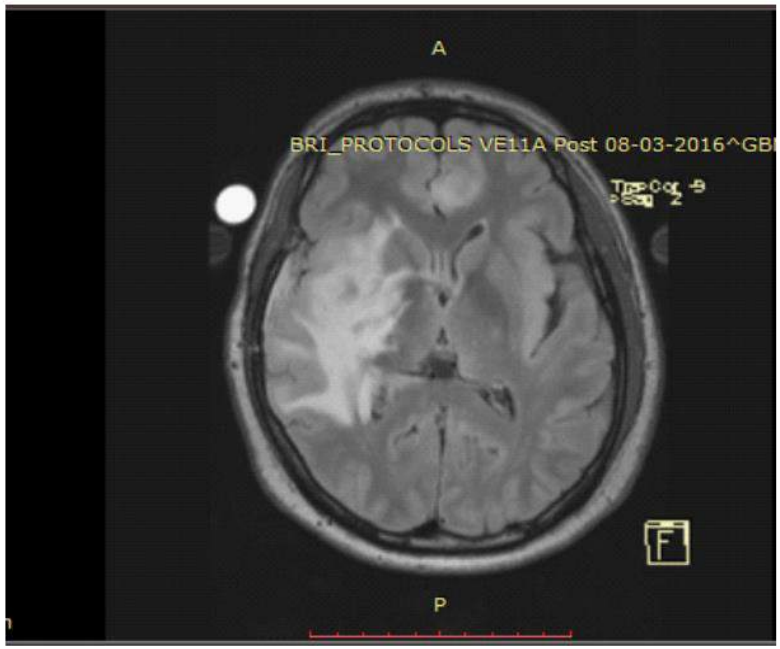
Subject 1301 - treated for **10 cycles** and completed trial due to PD. Up to **525 days** of survival was confirmed from survival follow up data after database locking

Treatment benefit has been demonstrated in a significant improvement in overall survival (~ 5 - 13+ months) from these patients by recursive partitioning analysis

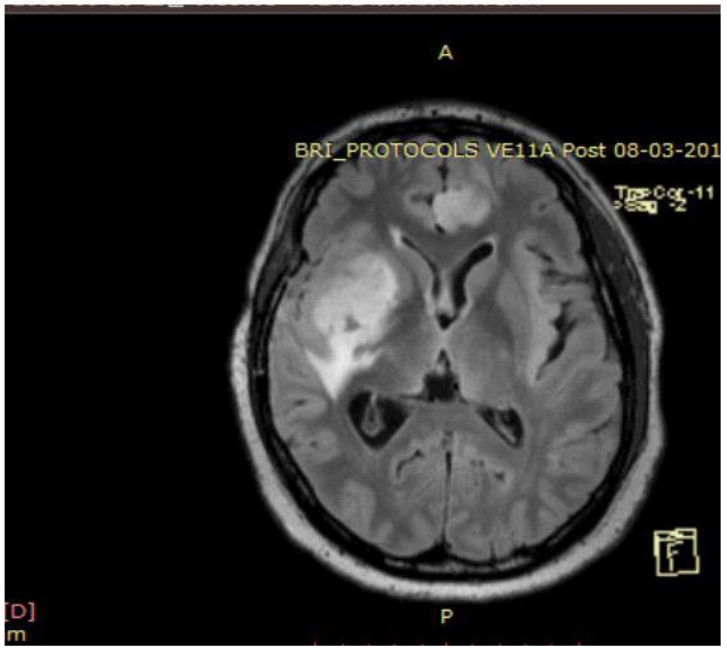
Brain edema which is commonly occurred to GBM patients was assessed by DCE-MRI. It was reduced in **5 subjects**.

Cerebral Edema was reduced after Olinvacimab treatment (Brain MRI)

Before



After



- 25 % disease control rate (up to 16 months)
- 42 % patients showed relief of brain edema
- 17 % patients reduced their use of corticoid-steroid
- Confirmed up to 525 days of overall survival

Olinvacimab ODD for both GBM and rGBM granted by FDA

FDA Orphan Drug Designation

Business Wire
A Berkshire Hathaway Company

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PharmAbcine Announces FDA Orphan Drug Designation Granted to TTAC-0001 for Glioblastoma Multiforme

April 01, 2018 06:00 PM Eastern Daylight Time

DAEJEON, South Korea--(BUSINESS WIRE)--PharmAbcine Inc., a clinical-stage biotech company developing novel antibody therapeutics for multiple cancer indications, announced today that U.S. Food and Drug Administration (FDA) has granted orphan drug designation to its leading clinical compound TTAC-0001 for "treatment of Glioblastoma Multiforme."

https://www.businesswire.com/news/home/20180401005001/en/PharmAbcine-Announces-FDA-Orphan-Drug-Designation-Granted

Olinvacimab Phase II Avastin refractory rGBM IND approved by FDA

PharmAbcine Announces FDA Accepts IND Application of TTAC-0001 for the Treatment of Recurrent Glioblastoma

October 02, 2018 12:40 AM Eastern Daylight Time

DAEJEON, South Korea--(BUSINESS WIRE)--PharmAbcine, Inc, a clinical-stage biotech company developing novel antibody therapeutics for multiple cancer indications announces that the company received "Study May Proceed Letter " from the US Food and Drug Administration (FDA) for the Investigational New Drug ("IND") application of its flagship antibody, TTAC-0001. This enables the Company to begin opening US clinical trial sites for phase II clinical trial with bevacizumab (Avastin®) refractory recurrent GBM patients.

"Study May Proceed Letter " from the US Food and Drug Administration (FDA) for the Investigational New Drug ("IND"

Tweet this

Recurrence of GBM is inevitable and recurrent GBM (rGBM) is one of the most aggressive and has the worst prognosis. The treatment options are limited with modest activity for rGBM. Therefore, there is no universally held standard of care available till now.

Patients with rGBM are suffering under cerebral edema and partially responded to bevacizumab. However, patients responded to bevacizumab ultimately become non-responder during the treatment and once patients become bevacizumab non-responder, unfortunately, there are no more therapeutic options.

https://www.businesswire.com/news/home/20181001006077/en/PharmAbcine-Announces-FDA-Accepts-IND-Application-TTAC-0001

AFTER EXECUTION of Olinvacimab + Keytruda combination

At JPMHC 2018 MERCK RECEPTION

https://en.wikipedia.org/wiki/Kenneth_Frazier

BUSINESS WIRE

BusinessWire
A Berkshire Hathaway Company

PharmAbcine Enters Collaboration with MSD Focused on Clinical Evaluation of TTAC-0001 in Combination with KEYTRUDA® (pembrolizumab) in Recurrent Glioblastoma and Breast Cancer

1 FEB 2018

Tweet

0 Like

G+

DAEJEON, South Korea

PharmAbcine Inc., a clinical-stage biotech company developing novel antibody therapeutics for multiple cancer indications, announces it has entered into a collaborative agreement with MSD (tradename of Merck & Co., Inc., Kenilworth, N.J., USA), through a subsidiary, to evaluate PharmAbcine's anti-VEGFR2 mAb, TTAC-0001, in combination with MSD's anti-PD-1 (programmed death receptor-1) therapy, KEYTRUDA® (pembrolizumab), in patients with recurrent glioblastoma multiforme (rGBM) and metastatic triple-negative breast cancer (TNBC).

PharmAbcine's lead candidate TTAC-0001, an investigational therapy, is a highly selective and potent anti-VEGFR2 (KDR/flk-1) mAb in clinical development for rGBM indications. VEGFR2 is over-expressed in most malignant tumors, such as gastric, liver,

https://www.businesswire.com/news/home/20180201005016/en/PharmAbcine-Enters-Collaboration-MSD-Focused-Clinical-Evaluation

COGNO
COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

12th COGNO Annual Scientific Meeting
The Neuro-Oncology Picture: Now and The Future

Sunday 27th October – Tuesday 29th October 2019
International Convention Centre Sydney, Australia

Olinvacimab + Pembrolizumab in rGBM Interim Result (June 2020)

- Safety
  - No DLT
  - TEAE (treatment emergent adverse event) occurred to all patients
    - hemangioma, fatigue, seizure, rash, blurred vision etc.
  - TEAE with CTCAE Grade 3 – 7 events from 4 patients
    - weakness, seizure(2), aspiration pneumonia, elevated LFTs, blurred vision, fatigue
    - Grade 3 AE related to treatment – 1 event (fatigue)
    - SAE – 6 events from 4 patients
      - - seizure(5), hydrocephalus
  - Hemangioma – occurred from 6 patients (67%)
    - - Grade 1 - 15 events
    - - Grade 2 - 1 event
- Efficacy
  - **4 patients (44%) had stable disease as best response**
  - **1 patient is staying on SD over 12 cycles (currently 15 cycles, 10 months)**
  - **Median OS – 7.2 months (range 2.1-14.6 months)**
  - **Median PFS – 1.3 months (range 1.2-8.3 months)**

Olinvacimab + Pembrolizumab w/ mTNBC

LIVERPOOL HOSPITAL
Established 1813

Hollywood Private Hospital
Part of Ramsay Health Care

Olinvacimab + Pembrolizumab in mTNBC Interim Result (June 2020)

- Safety
  - No DLT
  - TEAE (treatment emergent adverse event) occurred to all patients
    - fatigue, nausea, rash, dizziness, headache, arthralgia, polyuria etc.
  - TEAE with CTCAE Grade 3 or more – 24 events from 5 patients

    - disease progression (2), hypertension (2), anemia(2), hypokalemia (2), myositis (2), pulmonary embolism, pleural effusion, pain, urinary track infection, ascites, ileus, hyperkalemia, sepsis, hemodynamic failure, weight loss, seizure, hypotension, fever, hyponatremia
  - Grade 3 AE related to treatment – 3 events (two Hypertension and one pulmonary embolism)
    - SAE – 7 events from 4 patients
      - - pain, disease progression(2), pulmonary embolism, seizure, hypotension, myositis
  - Hemangioma – occurred from 8 patients (73%)
    - - Grade 1 - 34 events
    - - Grade 2 - 13 event

Efficacy

- **4 patients (36%) had PR(partial response) as best response**
- **1 patient had CR in target lesion (overall PR due to non-target lesion remained)**
- **5 pts had clinical benefit (PR+SD≥24weeks).**
- **Median PFS – 4.2 months (range 0.5-10.7 months) as June, 2020.**
- **Expression level of PD-L1 is under investigation.**

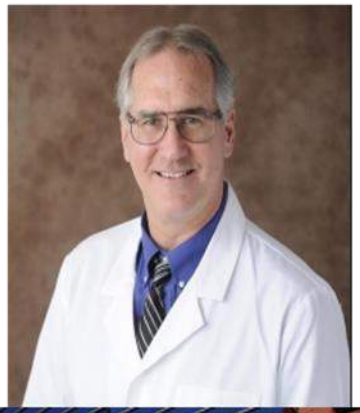
16mg/kg/w Olinvacimab for Phase II dose!

mTNBC (June 2020):

50% ORR

67% DCR

Olinvacimab Phase II Avastin non responding rGBM



Stanford University Cancer Center

Florida Cancer Center

https://www.biospace.com/article/pharmabcine-s-olinvacimb-able-to-manage-the-first-recruitment-of-patients-for-phase-ii-clinical-trial/

Olinvacimab clinical trials

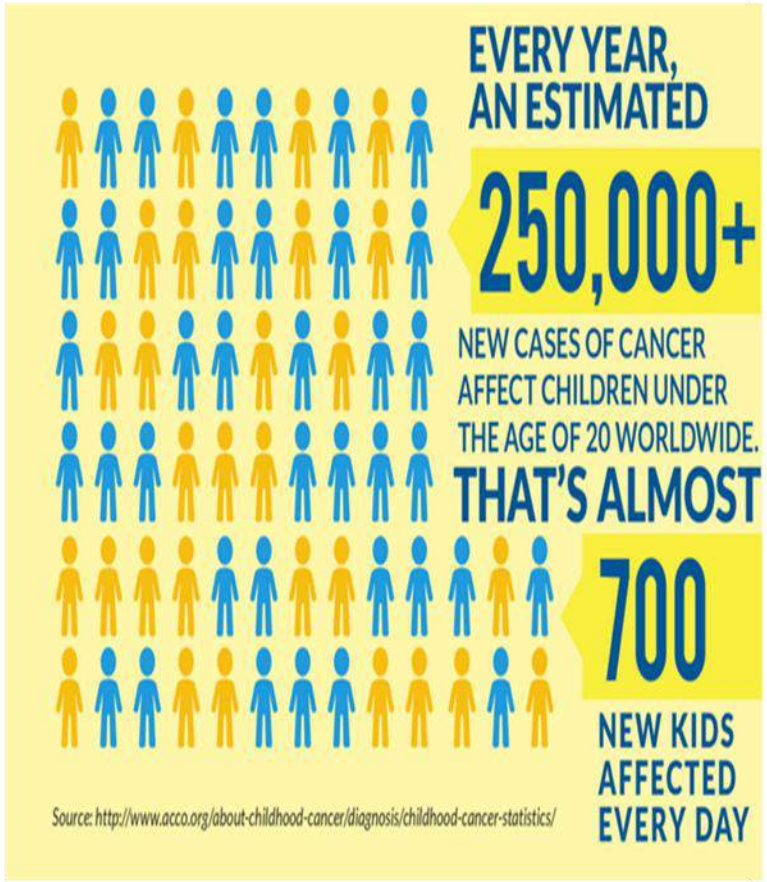
일시	국문	영문
2019.01.03	올린바시맙, 펨브로리주맙 병용투여 전이성 삼중음성유방암 호주 임상 1b상 FPFV(First Patient Fist Visit, 첫 환자등록)	FPFV (First patient First visit) on the study of Olinvacimab/Pembrolizumab combination trial for the treatment of mTNBC patients
2009.01.16	올린바시맙, 펨브로리주맙 병용투여 재발성 뇌종양 호주 임상 1b상 FPFV(First Patient Fist Visit, 첫 환자등록)	FPFV (First patient First visit) on the study of Olinvacimab/Pembrolizumab combination trial for the treatment of rGBM patients
2019.08.15	TTAC-0001, 재발성 뇌종양 다기관 국제 임상 호주 임상2상 HREC 승인	Approval Australia HREC of TTAC-0001 phase 2 study for the treatment of rGBM patient who has progressed after bevacizumab treatment
2019.08.27	TTAC-0001, 재발성 뇌종양 다기관 국제 임상 미국 임상2상 IRB 승인 (Stanford hospital)	Approval US IRB (Stanford Hospital) of TTAC-0001 phase 2 study for the treatment of rGBM patient who has progressed after bevacizumab treatment
2019.09.12	TTAC-0001, 재발성 뇌종양 다기관 국제 임상 미국 임상2상 IRB 승인 (Florida hospital)	Approval US IRB (Florida Hospital) of TTAC-0001 phase 2 study for the treatment of rGBM patient who has progressed after bevacizumab treatment
2019.11.13	TTAC-0001, 재발성 뇌종양 다기관 국제 임상 임상2상 FPFV(First Patient Fist Visit, 첫 환자등록)	Approval of TTAC-0001 phase 2 for Avastin ® - refractory rGBM Patients FPFV(First Patient Fist Visit)

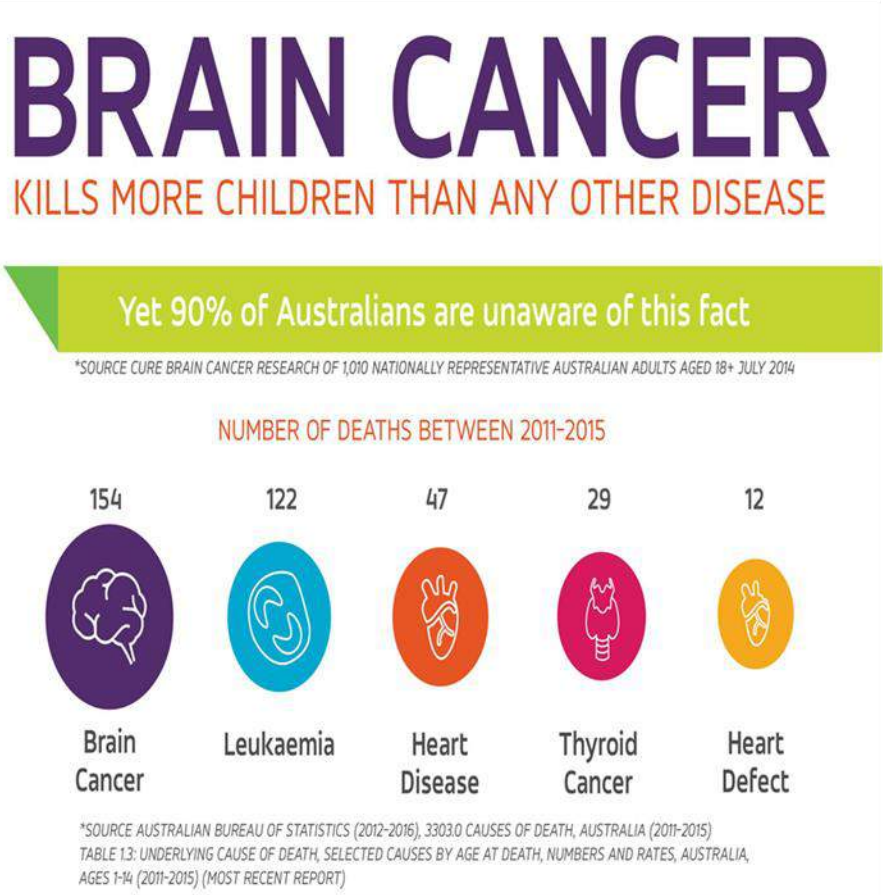
Plan for Clinical Trials

Olinvacimab + Pembrolizumab : ACC, mTNBCBM, TNBC, Stomach Cancer, etc.

Olinvacimab + Chemo combos : Stomach Cancer, TNBC, Ovarian Cancer, Colon Cancer, etc.

Olinvacimab with the Superior Safety Profile will Open New Trials with Pediatric Cancer Patients





Olinvacimab alone or its Combo

for

COVID-19 patients?

Clinical trials are currently underway to investigate the effectiveness of bevacizumab for the treatment of COVID-19, with results expected as early as May 2020.

The outbreak and rapid spread of the novel coronavirus, COVID-19, has resulted in the worldwide search for a viable treatment option. There are several drug candidates currently being investigated to treat COVID-19, such as remdesivir, ritonavir/lopinavir, and hydroxychloroquine. Another drug that is receiving significant attention in the fight against COVID-19 is bevacizumab.

Bevacizumab is a drug that is currently used to treat cancer (colorectal, lung, breast, renal, brain, and ovarian), as well as age-related macular degeneration and diabetic retinopathy. This drug has been used as an anti-tumour treatment for almost 20 years, so the safety of the drug is already known. Some of the most common adverse reactions to bevacizumab include hypertension, fatigue, diarrhea, and abdominal pain.

Bevacizumab is a human monoclonal antibody that works by attaching to a growth factor called vascular endothelial growth factor A (VEGF-A). By blocking the activity of this growth factor, the drug is able to inhibit the process of angiogenesis (formation of new blood vessels), which is an important process in cancer development.

https://medicalnewsbulletin.com/bevacizumab-for-the-treatment-of-covid-19/
https://medshadow.org/can-avastin-treat-covid-19/
https://www.roche.co.kr/content/pdf/Avastin_20170508_1_0.pdf
https://www.lilly.co.kr/kr/product-information/oncology/cyramza-injection.aspx

Olinvacimab for Pulmonary Edema with or without COVID-19

What's the evidence to support using bevacizumab for the treatment of COVID-19?

The basis for using bevacizumab to treat COVID-19 comes from research that has identified elevated levels of VEGF in the blood of patients with COVID-19. It has been suggested that the increase in levels of VEGF is due to hypoxia (low oxygen) and severe inflammation, with evidence that VEGF plays a key role, and is therefore a prime treatment target, in acute lung injury and acute respiratory distress syndrome. Prior research suggests that suppression of VEGF could suppress pulmonary edema (accumulation of fluid in the lungs leading to respiratory failure), thereby reducing overall mortality in patients with severe COVID-19 infection.

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Efficacy and tolerability of bevacizumab in patients with severe Covid -19

Jiaojiao Pang, Feng Xu, Gianmarco Aondio, Yu Li, Alberto Fumagalli, Ming Lu, Giuseppe Valmadre, Jie Wei, Yuan Bian, Margherita Canesi, Giovanni Damiani, Yuan Zhang, Dexin Yu, Jun Chen, Xiang Ji, Wenhai Sui, Bailu Wang, Shuo Wu, Attila Kovacs, Miriam Revera, Hao Wang, Ying Zhang, Yuguo Chen, Yihai Cao

doi: https://doi.org/10.1101/2020.07.26.20159756

On the basis of Covid-19-induced pulmonary pathological and vascular changes, we hypothesized that the anti-VEGF drug bevacizumab might be beneficial for treating Covid-19 patients. We recruited 26 patients from 2-centers (China and Italy) with confirmed severe Covid-19, with respiratory rate ≥30 times/min, oxygen saturation ≤93% with ambient air, or partial arterial oxygen pressure to fraction of inspiration O2 ratio (PaO2/FiO2) >100mmHg and ≤300 mmHg, and diffuse pneumonia confirmed by chest radiological imaging. This trial was conducted from Feb 15 to April 5, 2020, and followed up for 28 days. Relative to comparable control patients with severe Covid-19 admitted in the same centers, bevacizumab showed clinical efficacy by improving oxygenation and shortening oxygen-support duration. Among 26 hospitalized patients with severe Covid-19 (median age, 62 years, 20 [77%] males), bevacizumab plus standard care markedly improved the PaO2/FiO2 ratios at days 1 and 7 (elevated values, day 1, 50.5 [4.0,119.0], p<0.001; day 7, 111.0 [85.0,165.0], p<0.001). By day 28, 24 (92%) patients showed improvement in oxygen-support status, 17 (65%) patients were discharged, and none showed worsen oxygen-support status nor died. Significant reduction of lesion areas and ratios were shown in chest CT or X-ray analysis within 7 days. Of 14 patients with fever, body temperature normalized within 72 hours in 13 (93%) patients. Lymphocyte counts in peripheral blood were significantly increased and CRP levels were markedly decreased as shown in available data. Our findings suggested bevacizumab plus standard care was highly beneficial for treating patients with severe Covid-19. Clinical efficacy of bevacizumab warrants double blind, randomized, placebo-controlled trials.

https://www.medrxiv.org/content/10.1101/2020.07.26.20159756v1

Potential Risk and Limitation of Avastin for COVID-19 patients

The hypertension and other side effects of Avastin will limit their clinical value for COVID-19/ARDS patients.

https://clinicaltrials.gov/ct2/show/NCT04275414
https://clinicaltrials.gov/ct2/show/NCT04305106
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7105280/

PharmAbcine is in the discussion with potential Principal Investigators in UK, US and other countries for

“Olinvacimab + Standard Care + Low Dose Dexamethasone phase II for COVID-19 with ARDS.”

Olinvacimab with Remdesivir, vaccine, or neutralizing antibody combo may be another option.

We are looking for collaborative partner for these topics.

We truly thank to :

Patients,

Caregivers,

PIs,

Medical staffs,

CRO staffs,

Advisors,

Investors

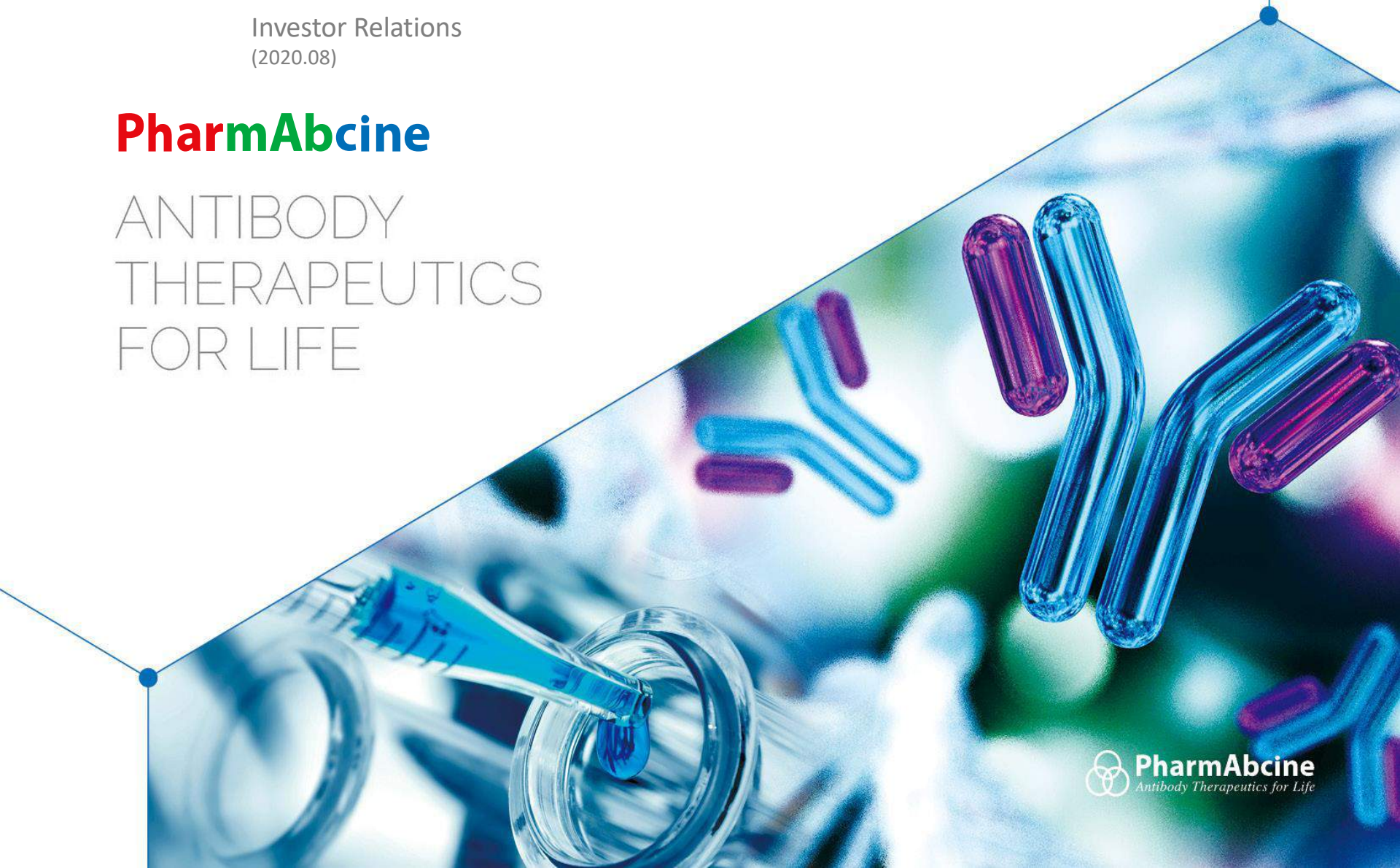
and

specially MSD!

Investor Relations
(2020.08)

PharmAbcine

ANTIBODY THERAPEUTICS FOR LIFE



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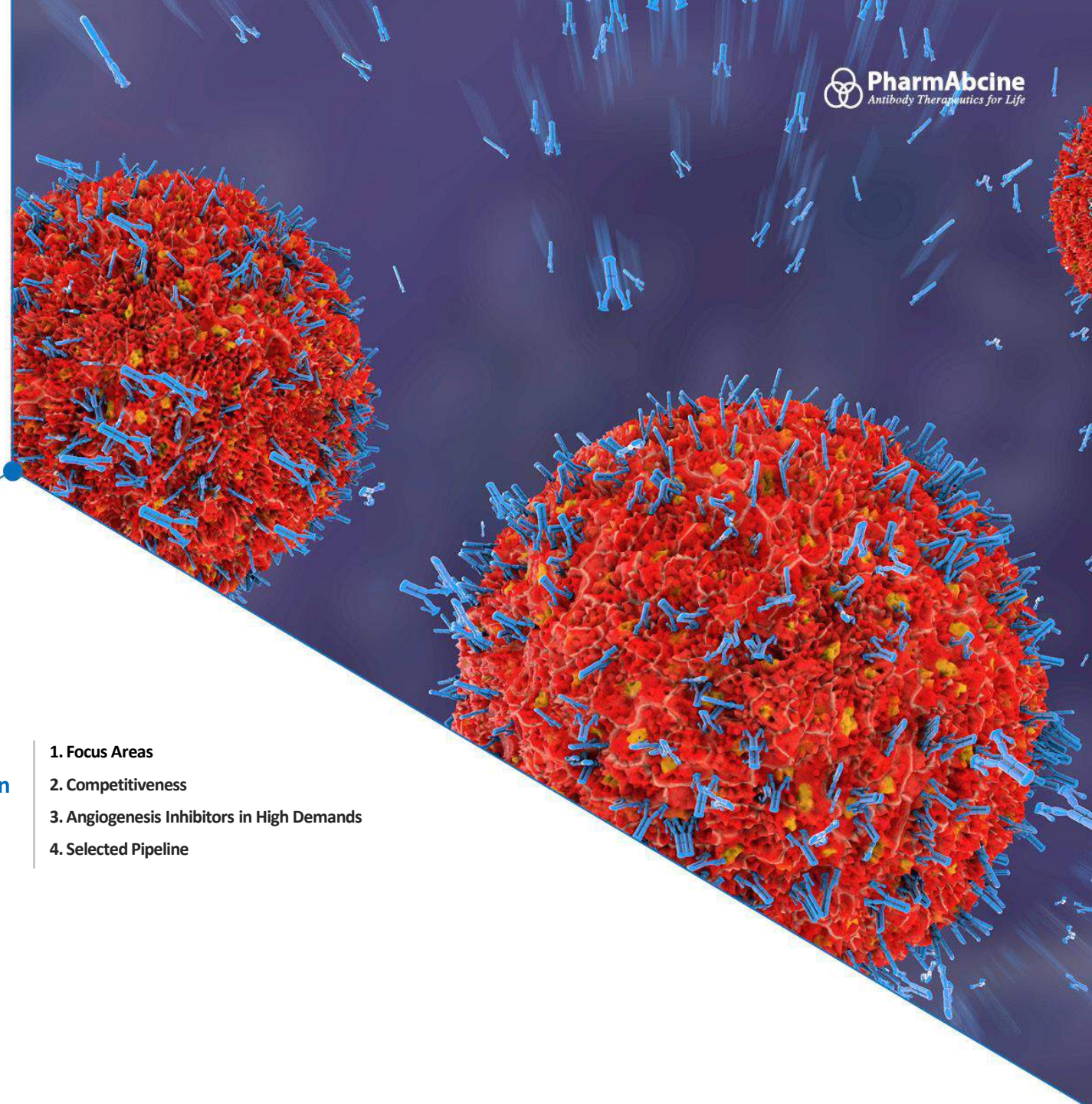
ANTIBODY
THERAPEUTICS
FOR LIFE

PharmAbcine

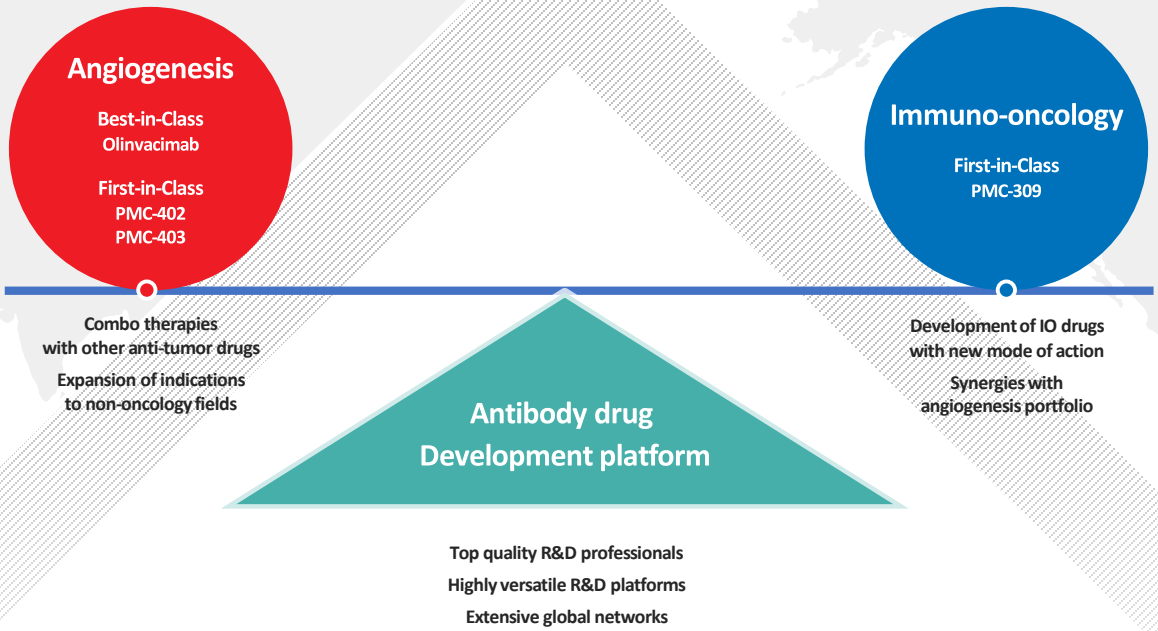


Company Introduction

PharmAbcine
Antibody Therapeutics for Life

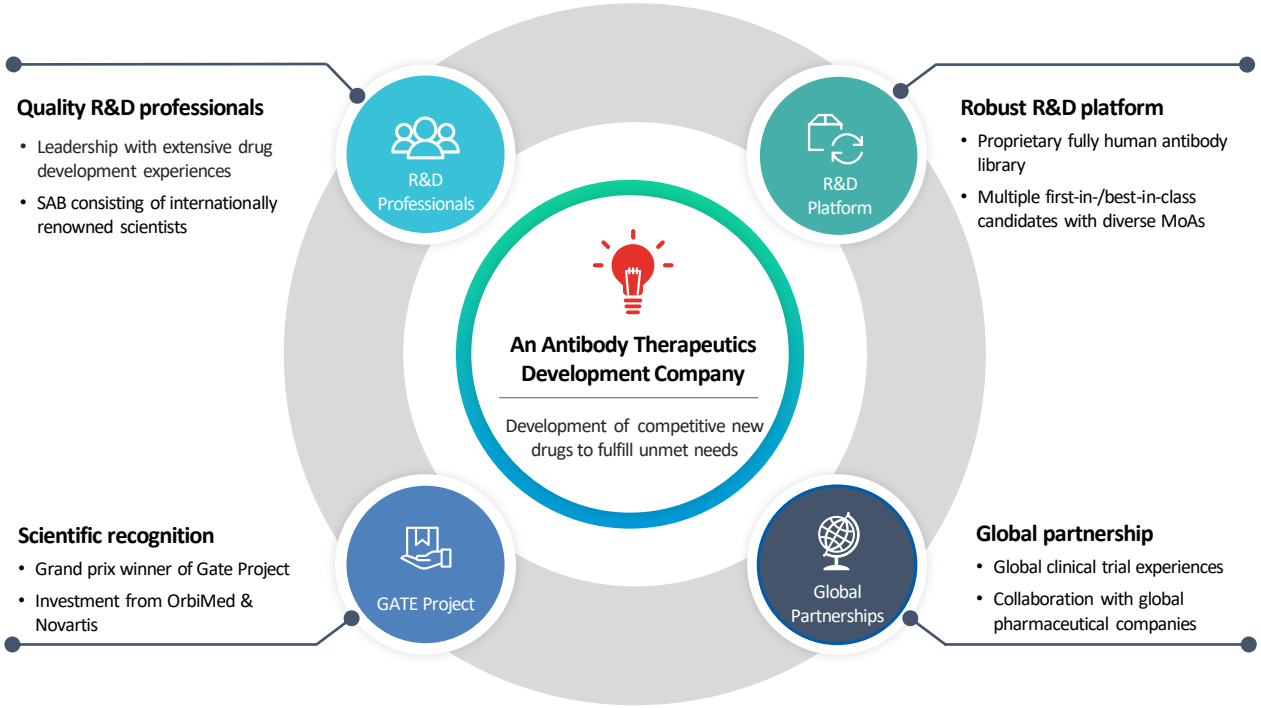
1. Focus Areas

Two pillars of antibody drug development: 1) Angiogenesis and 2) Immuno-oncology



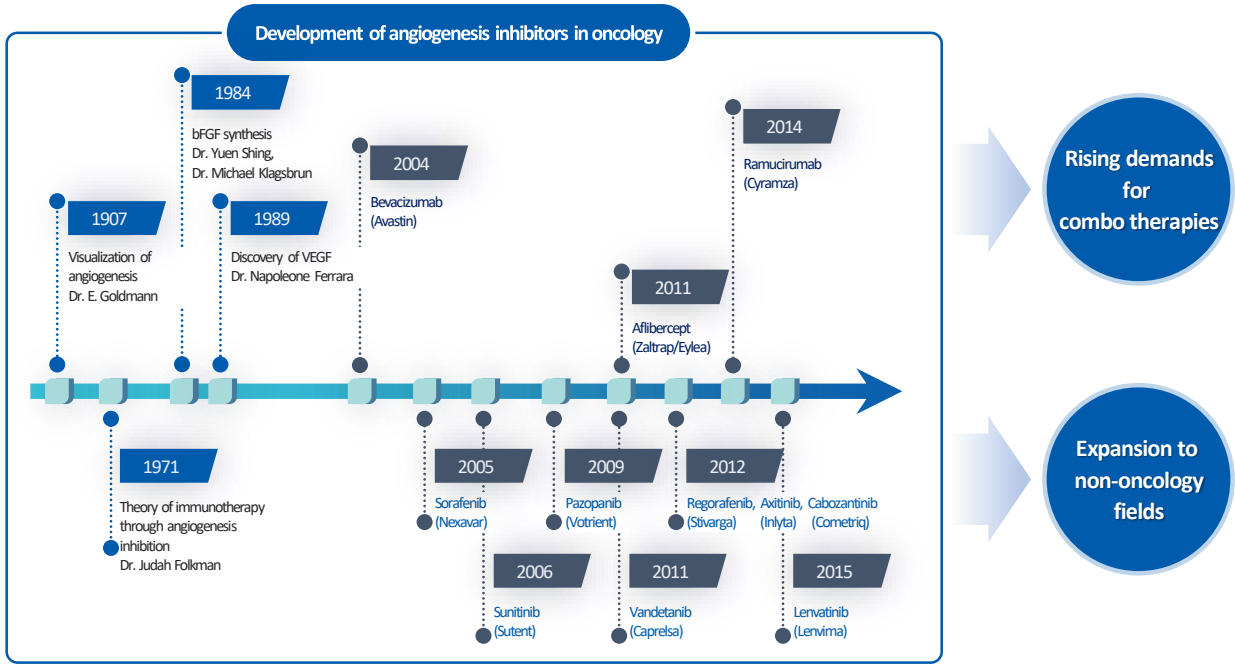
2. Competitiveness

"A clinical-stage antibody therapeutics development platform company"



3. Rising Demands for Angiogenesis Inhibitors

Oldies but goodies



4. Selected Pipeline

Molecules	Mode of Action	Indications	Lead Compound	Preclinical	Phase I	Phase II	Phase III
Olinvacimab	anti-VEGFR2	rGBM	Australia				Early Commercialization Through ODD Designation
			Phase IIa Completed & Phase IIb In preparation				
		Avastin-refractory rGBM	U.S, Australia				
		Solid tumors	IIT(Investigator Initiated Trial) for various solid tumors in preparation				
Olinvacimab + Keytruda®	anti-VEGFR2 + anti-PD1	mTNBC	Australia			*Phase II in preparation*	
		rGBM	Australia				
PMC-402	Tie2 activator	Solid tumors	*Phase I in 2021*				
PMC-403	Tie2 activator	Ocular diseases	*Phase I in 2022*				
PMC-309	anti-VISTA	Solid tumors	*Phase I in 2021*				

- Discovery-stage assets are not presented here (refer to p.47)
- rGBM: Recurring Glioblastoma Multiforme
- mTNBC: Metastatic Triple Negative Breast Cancer

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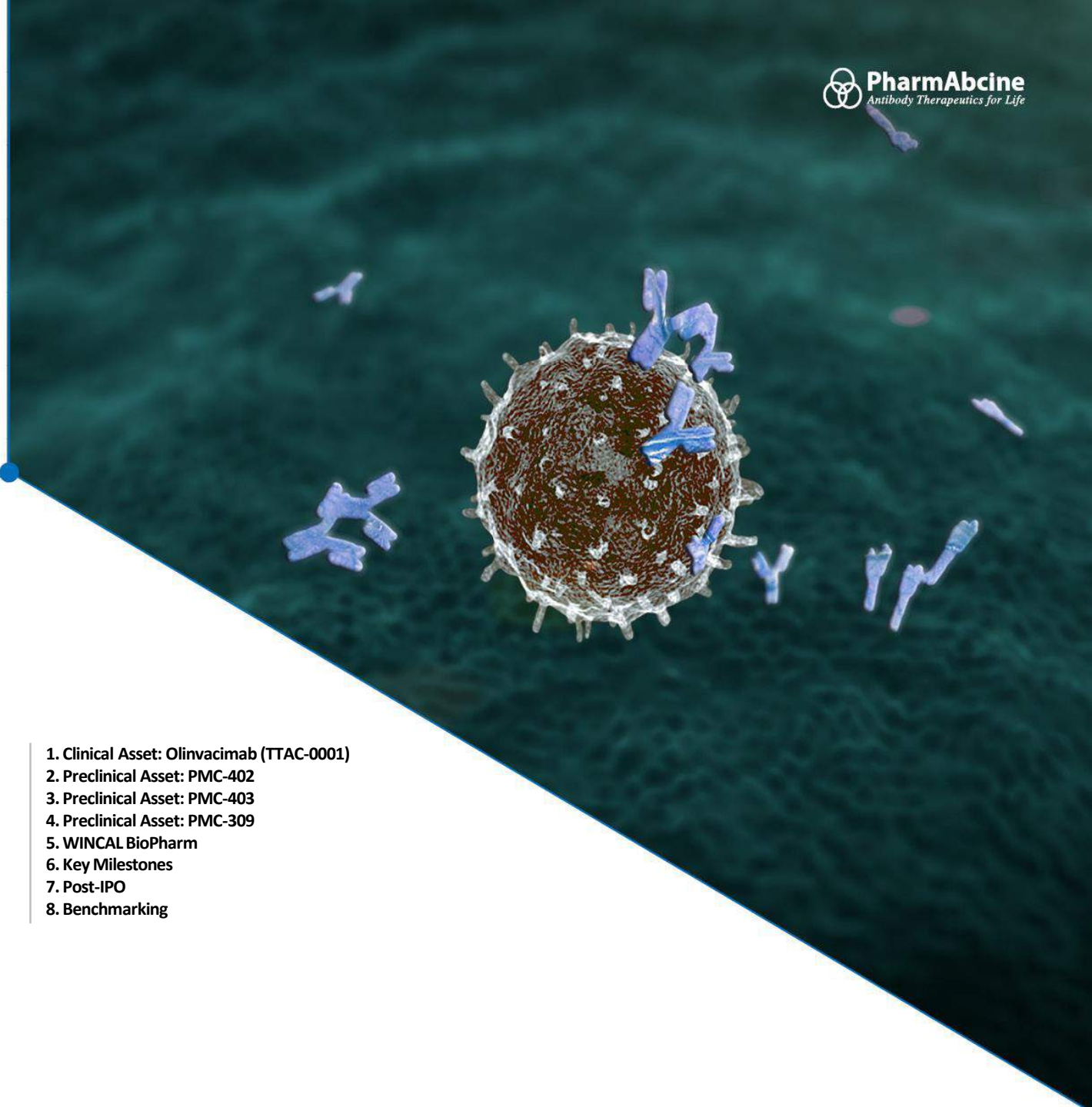


R&D Pipeline

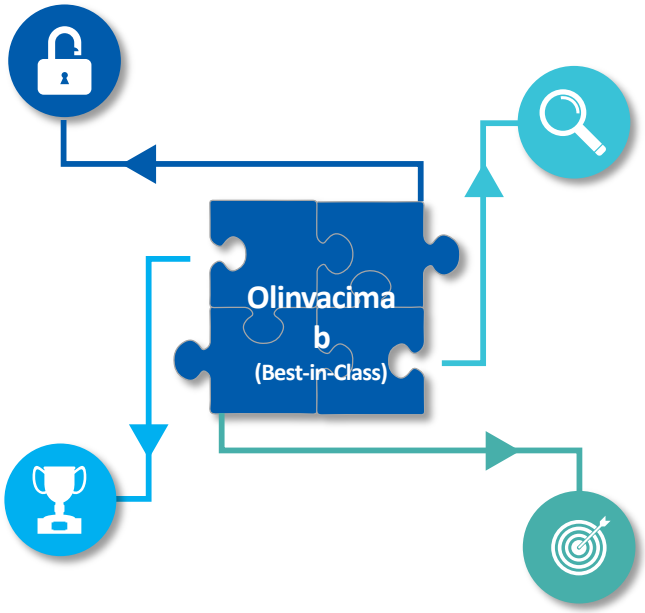
1. Clinical Asset: Olinvacimab (TTAC-0001)
2. Preclinical Asset: PMC-402
3. Preclinical Asset: PMC-403
4. Preclinical Asset: PMC-309
5. WINCAL BioPharm
6. Key Milestones
7. Post-IPO
8. Benchmarking

1. Clinical Asset: Olinvacimab 1) Introduction

Best-in-class potential in terms of safety & efficacy profile

Mode of Action

Inhibits tumor angiogenesis & modulates TME by targeting VGFR-2



Current Clinical Trials

Phase II: mono
- Avastin-refractory rGBM

Phase 1b: combo with pembrolizumab
- mTNBC
- rGBM

Competitiveness

Superior safety and efficacy profile

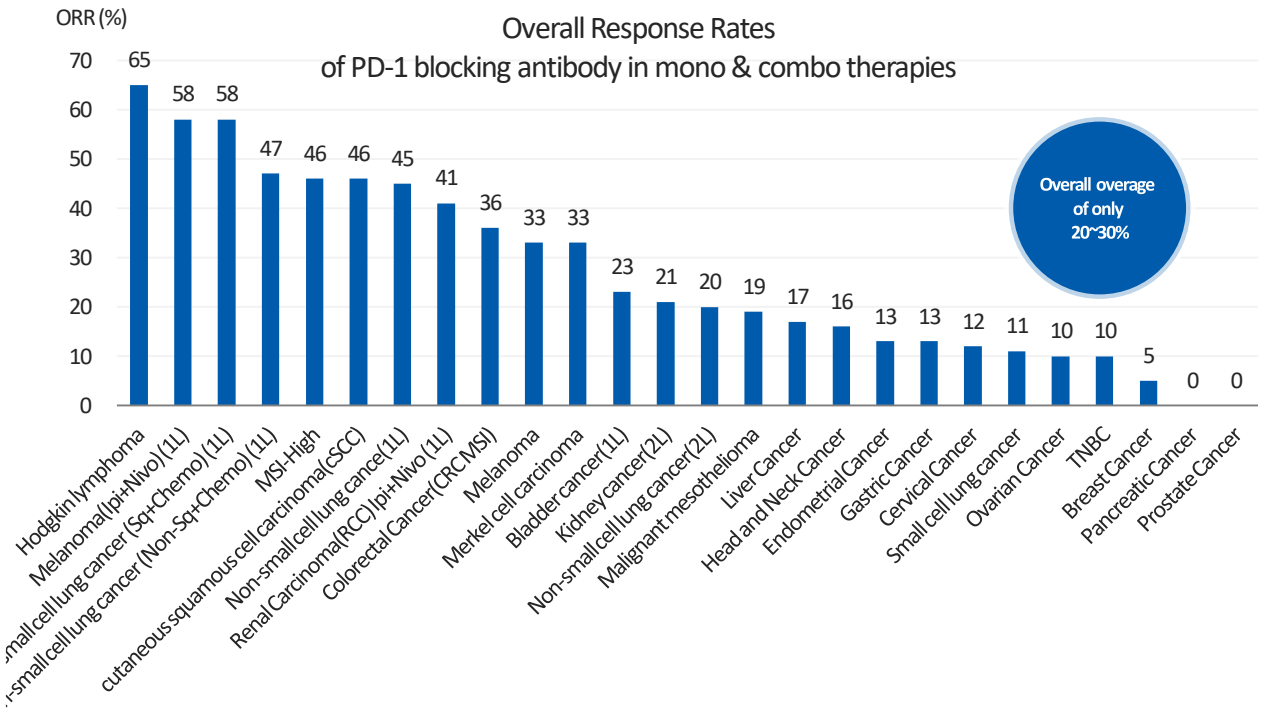
Development Strategy

To concentrate on mTNBC for existing combo therapies

To actively seek expansion of indications for both mono and combo therapies

1. Clinical Asset: Olinvacimab 2) Development Strategy

Low response rates mean new opportunities for biotech companies



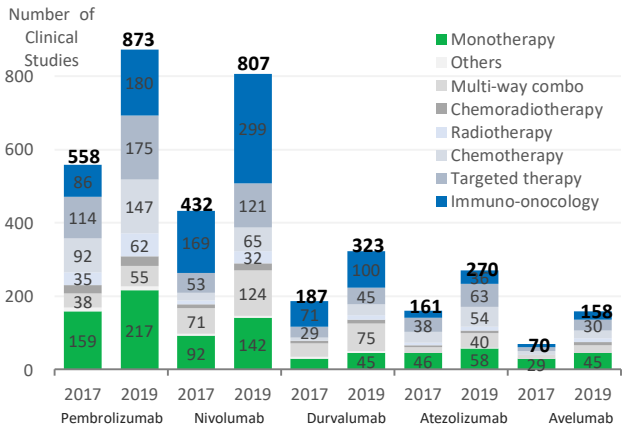
1. Clinical Asset: Olinvacimab 2) Development Strategy

Increasing combo therapies with PD-1 antibody means business for angiogenesis companies

▸ **Keytruda® (Immune Checkpoint Inhibitor)**

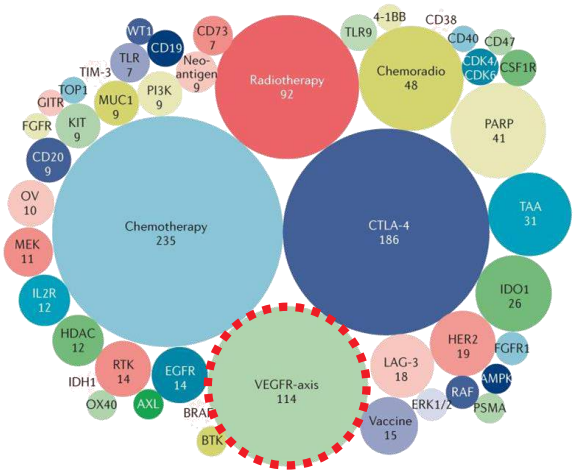
- U$72b in revenue in 2019 and predicted to be #1 drug by 2025
- Anti-PD-1 antibody can restore anti-tumor effects of T cells

A sharp rise in global trials of immune checkpoint inhibitors



Nature Reviews Drug Discovery **19**, 163-164 (2020)

VGFR-axis is the 3rd most popular combo studies

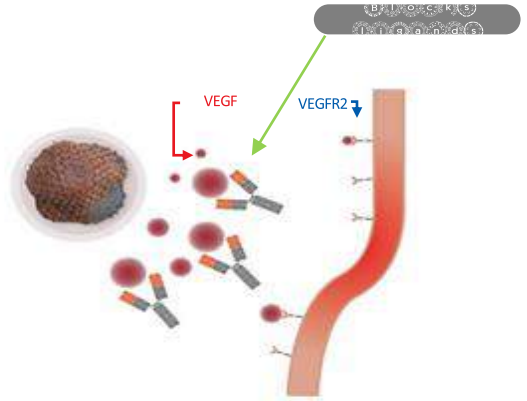


1. Clinical Asset: Olinvacimab 3) Mode of Action

Targeting the receptor, not the ligand, has its own benefits

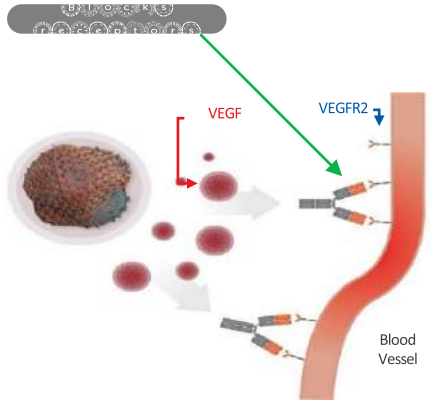
VEGF - ligand targeting

- **Avastin** : targets VEGF-A only
- **Zaltrap** : targets VEGF, PlGF
- Avastin does not completely inhibit angiogenesis as VEGF-C and VEGF-D are not blocked



VEGFR2 – receptor targeting

- **Olinvacimab** : targets VEGFR2 and completely suppresses VEGF signaling
- Eli Lilly's **Cyramza** has been approved for gastric, lung, and colon cancer and aims to replace Avastin in other indications as well



* TME: Tumor Microenvironment

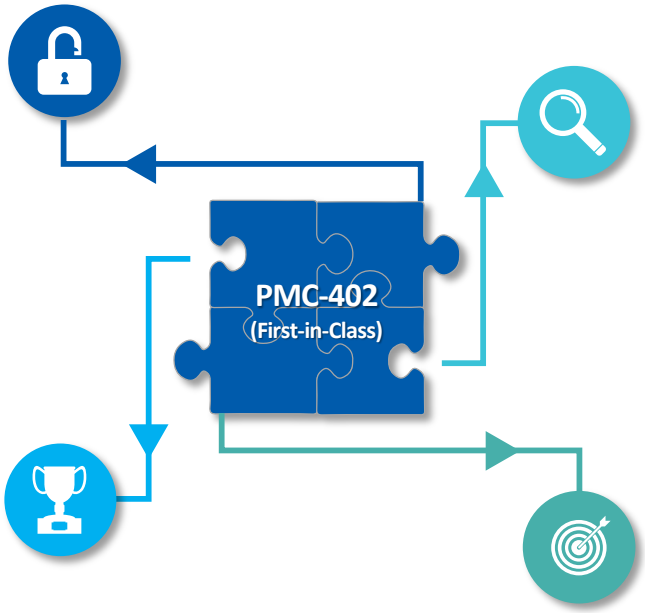
1. Clinical Asset: Olinvacimab 4) Superior to Competitors

We believe olinvacimab has a superior efficacy and safety profile

Product	Olinvacimab	Avastin *bevacizumab*	Cyramza *ramucirumab*	Zaltrap *aflibercept*
Structure	Fully Human Antibody	Humanized Antibody	Fully Human Antibody	Fc Fusion Protein
Fc-subtype	IgG1	IgG1	IgG1	IgG1
Mode of Action	KDR(VEGFR2)	VEGF-A	KDR(VEGFR2)	VEGF-A, PlGF
Signal Inhibition	VEGF-A,-C,-D	VEGF-A	VEGF-A,-C,-D	VEGF-A, PlGF
Affinity	2.3×10^{-10}	5×10^{-10}	3.8×10^{-10}	4.9×10^{-12}
Development Phase	Clinical Phase II	FDA Approval (2004)	FDA Approval (2014)	FDA Approval (2012)
Indications	mTNBC, rGBM	CRC, Renal C, Gastric C, NSCLC, GBM	Gastric C, CRC, Hepatic C, NSCLC	CRC
Revenue (2019)	-	7.3 Billion USD	930 Million USD	97 Million Euro (Sanofi)
Side Effects	Reversible capillary hemangioma In Grade 1-2	Hypertension, Gastric/Lung perforation, Hemorrhage, or Proteinuria, etc.		

2. Preclinical Asset: PMC-402 1) Pipeline Introduction

PMC-402 has a strong first-in-class potential!



Mode of Action

Activates Tie2
Normalizes leaky vessel around tumor
Increased T cell infiltration

Clinical Development

Preclinical development in progress
- Signed CDMO with Samsung Biologics

Global phase I study in 2021

Competitiveness

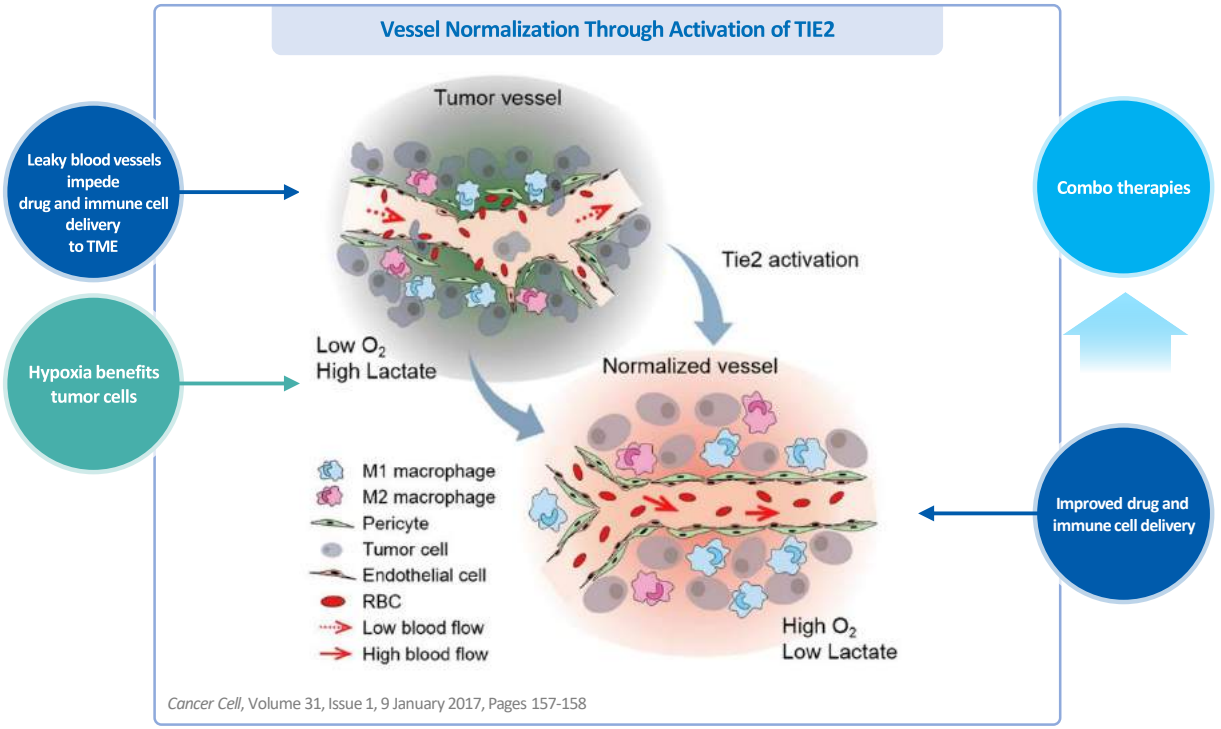
First-in-Class
Unique mode of action
Highly effective vessel normalizer
compared to current therapy

Development Strategy

Therapeutic uses in solid tumors
In combination with IO

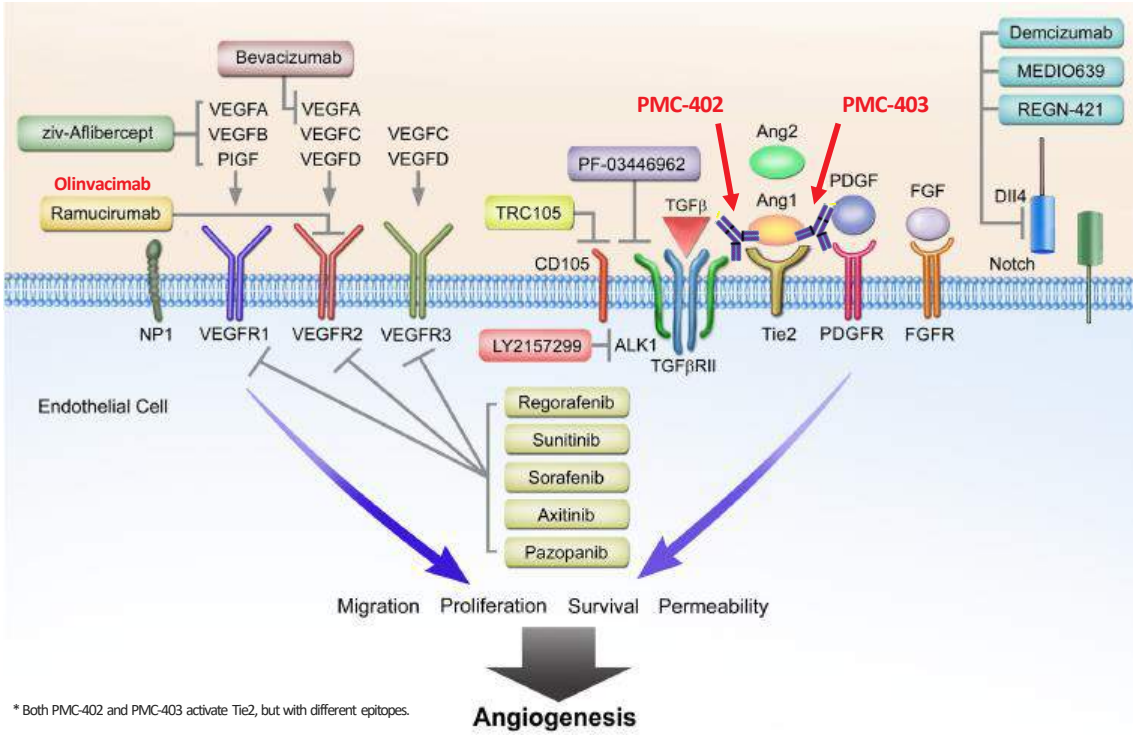
2. Preclinical Asset: PMC-402 2) Mode of Action

Vessel normalization improves drug and immune cell delivery to TME



3. Preclinical Asset: PMC-402 3) Development Strategy

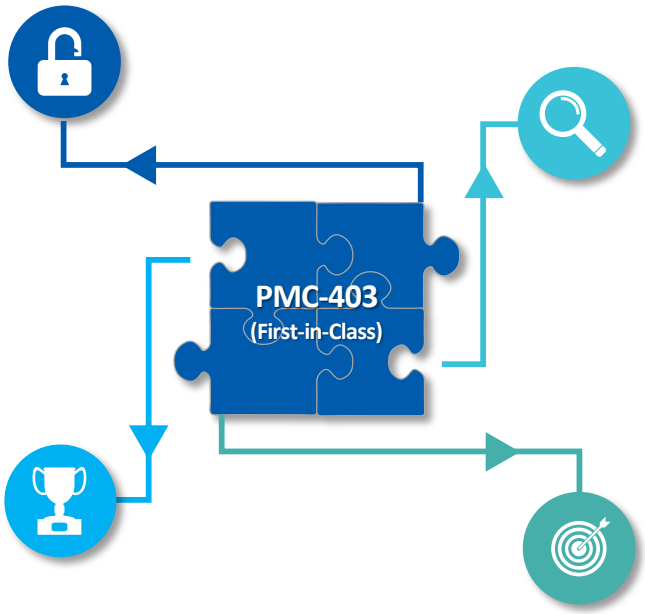
First-in-class potential thanks to a unique mechanism of binding directly to TIE2



* Both PMC-402 and PMC-403 activate Tie2, but with different epitopes.

3. Preclinical Asset: PMC-403 1) Pipeline Introduction

PMC-403 has a strong first-in-class potential too!



Mode of Action

Tie2 Activator
Vessel normalizer

Clinical Development

Preclinical development in progress
- Signed CDMO with Samsung Biologics

Global phase I study in 2022

Competitiveness

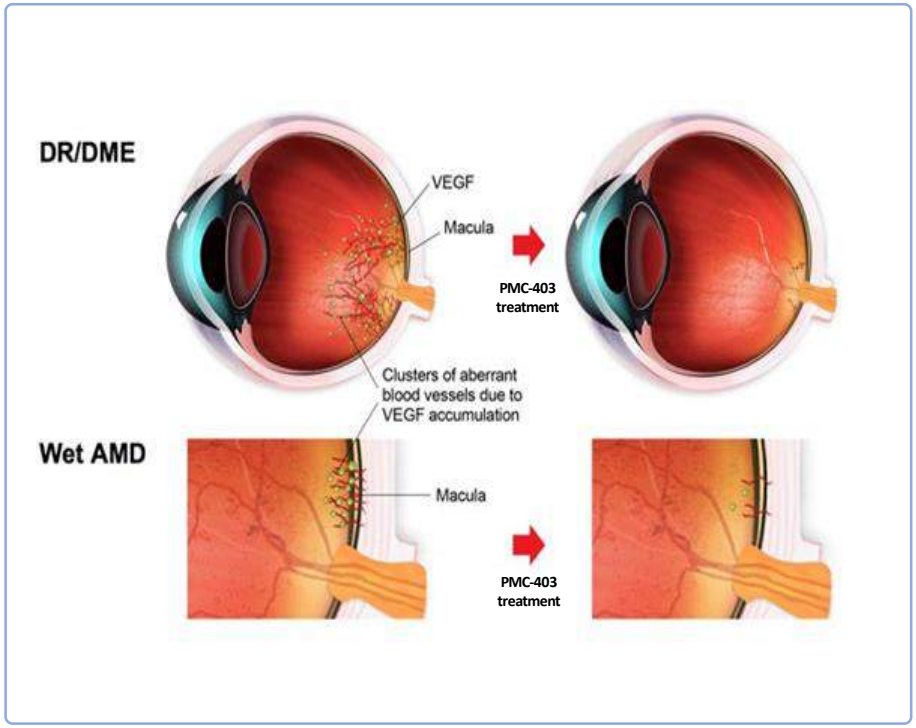
First-in-Class
Unique mode of action
Highly effective vessel normalizer compared to current therapy

Development Strategy

Confirmed efficacy in combo with IO drug in preclinical study
Therapeutic uses in vascular diseases including AMD, DR, ARDS, AKI, etc

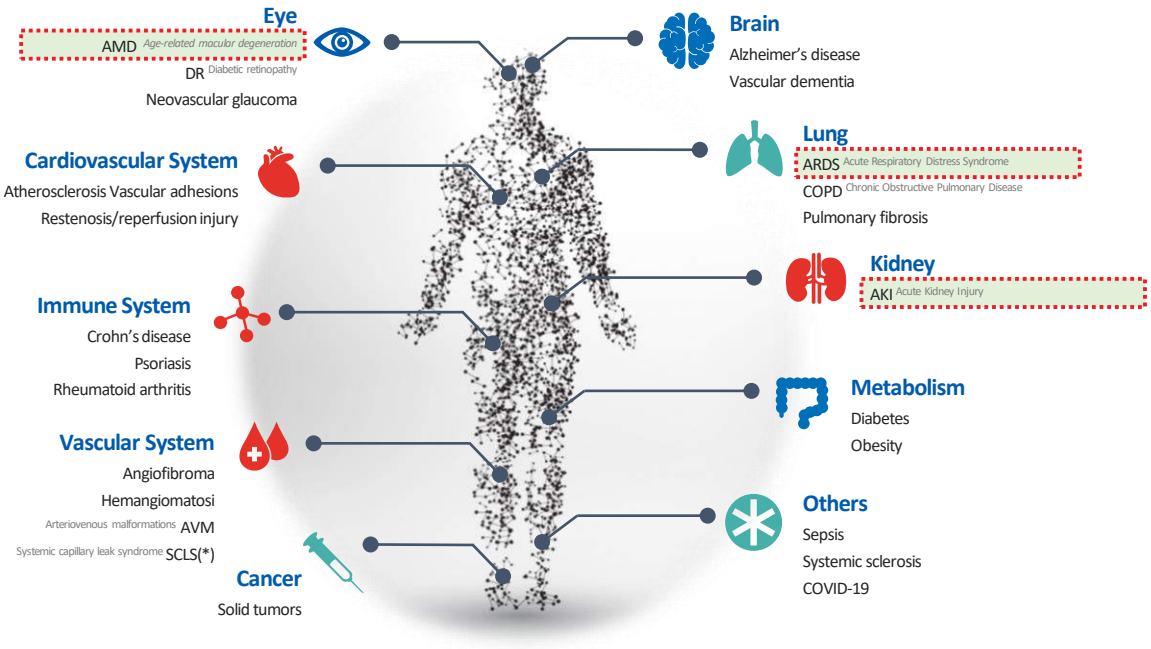
3. Preclinical Asset: PMC-403 2) Mode of Action

A strong candidate in AMD and DR therapeutics



3. Preclinical Asset: PMC-403 3) Development Strategy

Indications that PMC-403 could potentially be used

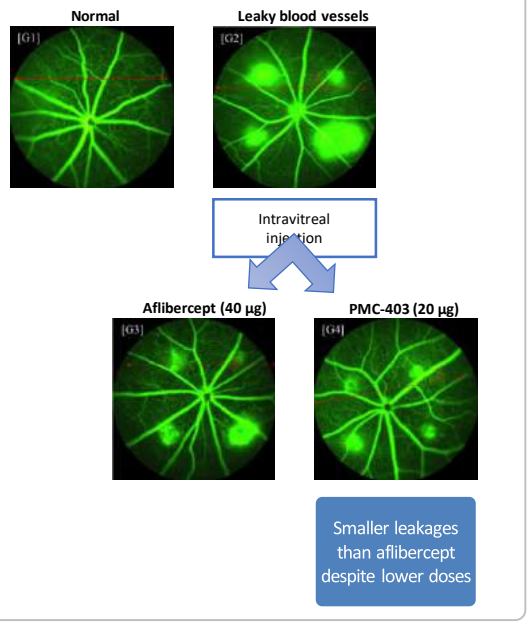


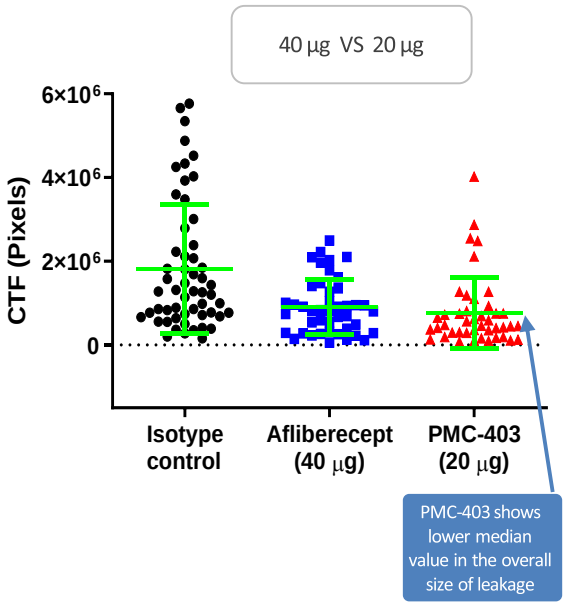
* Preclinical study with NIAID (National Institute of Allergy and Infectious Diseases), a suborganization of NIH

3. Preclinical Asset: PMC-403 4) Preclinical Results

PMC-403 shows better vessel leakage inhibition than Eylea® (aflibercept) even at lower doses

PMC-403 inhibits retinal leakage in laser-induced choroidal neovascularization (CNV) mouse model



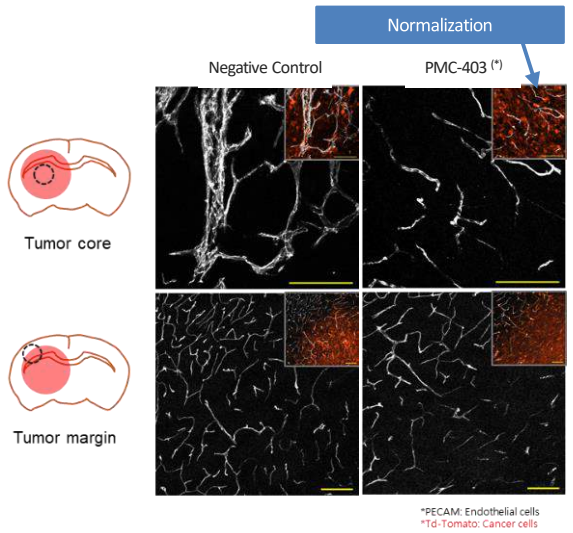


* CTF : Corrected Total Fluorescence

3. Preclinical Asset: PMC-403 4) Preclinical Results

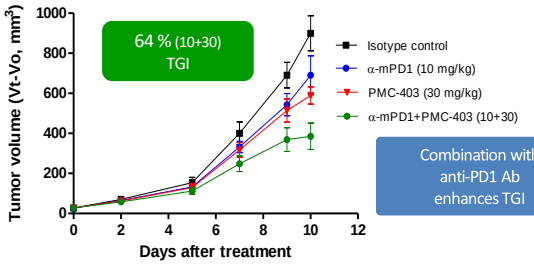
PMC-403 could improve delivery of an anti-PD1 Ab and enhance anti-tumor effects

PMC-403 normalizes murine brain tumor blood vessels

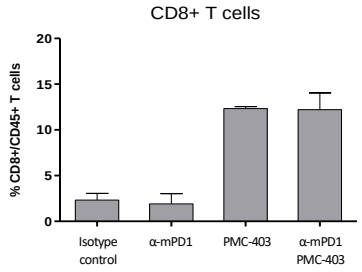


* PMC-403 binds to both human and mouse Tie2

Preclinical studies yielded desired results



Combination with anti-PD1 Ab enhances TGI

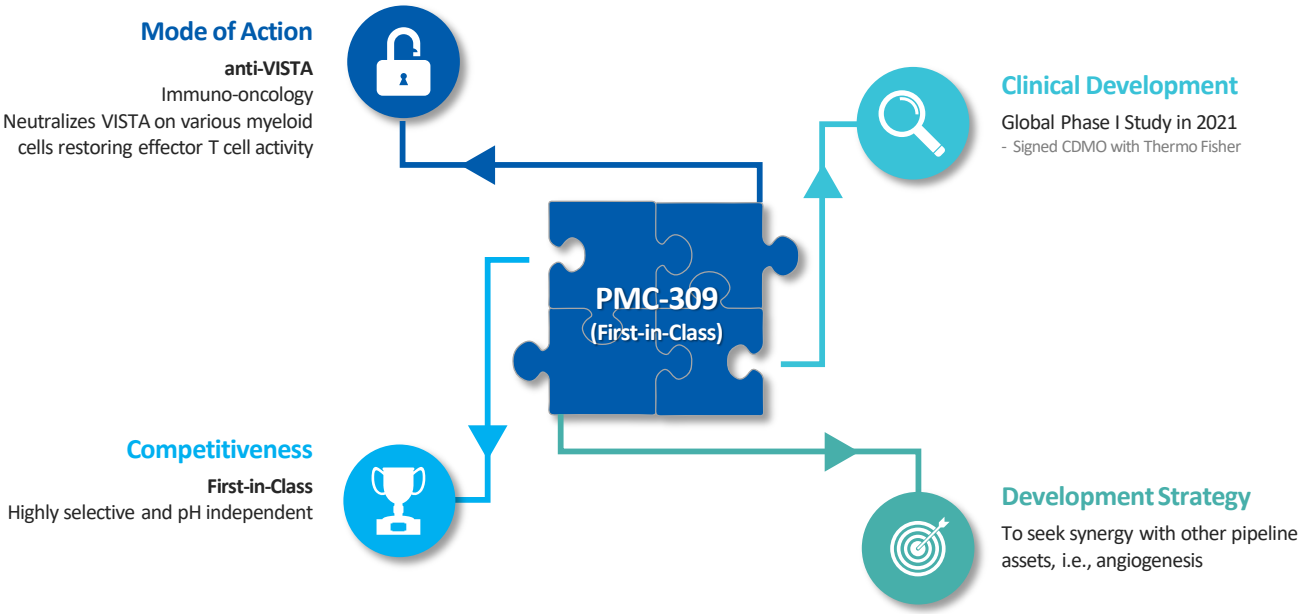


Improved T cell infiltration to TME correlates with TGI

* TGI: Tumor Growth Inhibition

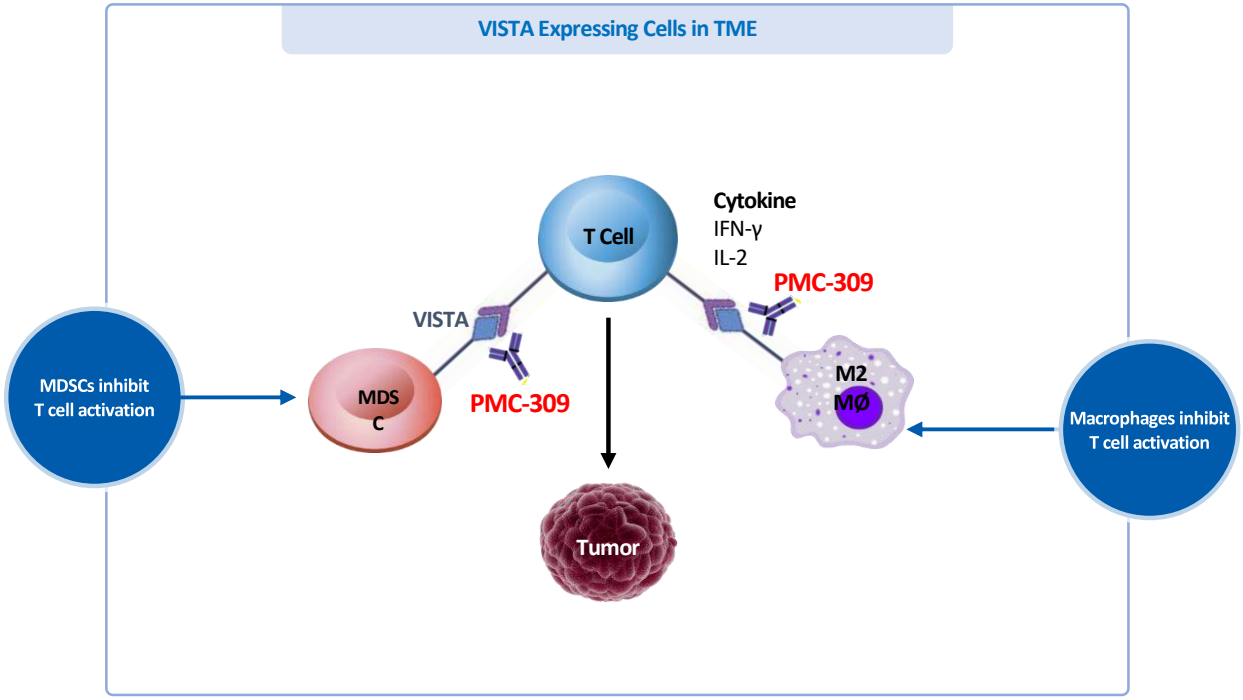
4. Preclinical Asset: PMC-309 1) Introduction and Development Plan

A first-in-class potential because PMC-309 is highly selective and pH independent



4. Preclinical Asset: PMC-309 2) Mode of Action

Anti-VISTA Ab restores immune activity of T cells through inhibition of VISTA interaction

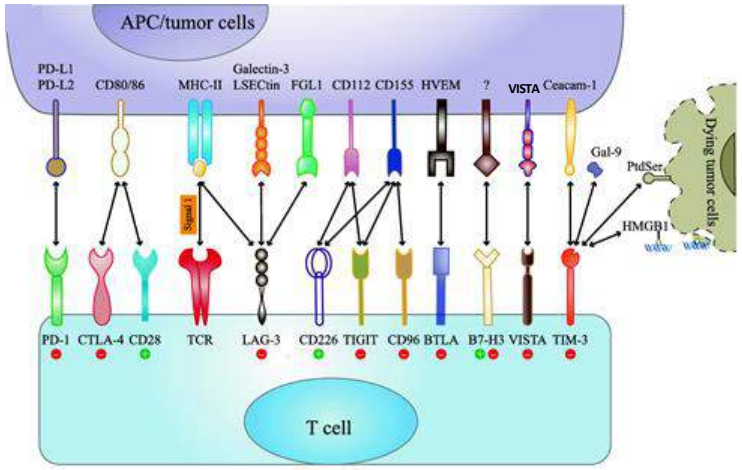


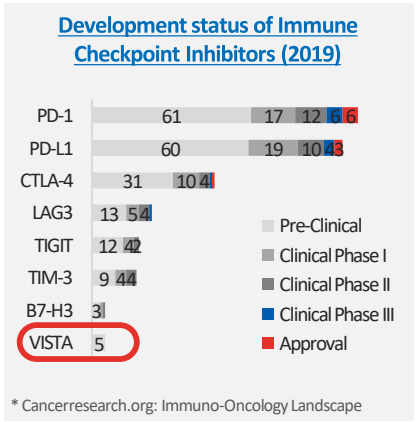
* MDSCs (Myeloid-derived suppressor cells) : Interact with T cells and inhibit immune response

4. Preclinical Asset: PMC-309 3) Development Strategy

Less players suggest early mover advantage

Immune checkpoint inhibitors with different MoAs





4. Preclinical Asset: PMC-309 3) Development Strategy

The competitive landscape looks good

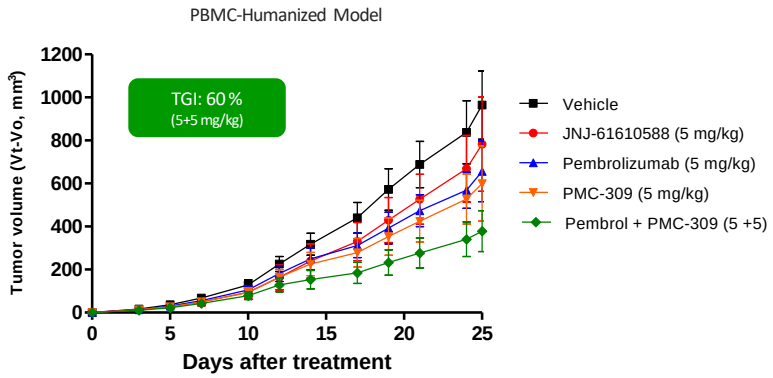
Company	Project	Clinical Phase	Remarks
Pierre Fabre Pharmaceuticals	K01401	Preclinical	License-in from Igenica (2017), AACR abstract (2019)
Curis	CI-8993	Preclinical	Licensed from ImmuNext
Hummingbird Bioscience	HMBD-002	Preclinical	SITC Abstract (2018), AACR abstract (2017, 2018)
Xcella Biosciences	VISTA	Preclinical	
Suzhou Stainwei Biotech	mAb-5	Preclinical	
Roche	VISTA Agonist	Preclinical	Licensed from ImmuNext
Boehringer Ingelheim	anti-VISTA IgG1 and IgG4	Preclinical	Announced in AACR (2019)
GigaGen	VISTA	Discovery	
Kineta	VISTA	Discovery	
Enumeral Biomedical	ENUM-007	Inactive	
ImmuNext	onvatilimab	Inactive	Licensed to J&J and Curis
Johnson & Johnson	JNJ-61610588	Inactive	Licensed from ImmuNext
BMS	VISTA	Inactive	Announced in AACR, and Nature (2019)
Bio-Thera Solutions	VISTA	Discovery	
Igenica	VISTA (C10orf54/IGN-381)	Inactive	AACR abstract (2016), Licensed to Pierre Fabre (2017)

* Only Antibody Drugs are shown
* Roche's main indications are in CNS and autoimmune diseases.

4. Preclinical Asset: PMC-309 4) Preclinical Results

PMC-309 shows synergy with pembrolizumab in an mTNBC model

Preclinical Results



Enhanced TGI with anti-PD1 mAb
▼
Suitable for pembrolizumab combo

* TGI: Tumor Growth Inhibition

5. Wincal Biopharm to provide platform for non-oncology fields

Unlocking the full value of PhamAbcine's pipeline assets and antibody discovery platform

WINCAL BioPharm

- A wholly owned US subsidiary of PharmAbcine
- Located in South San Francisco, USA

- Led by Dr. TaeWon Lee
- Staffed mostly with former AMGEN R&D professionals

- To focus on developing drugs for ophthalmology and vascular diseases using antibodies developed and/or owned by PharmAbcine

- New delivery technology platform: non-invasive methods (i.e. eye drop)

6. Key Milestones

Pipeline	2020	2021	2022
Olinvacimab (Mono therapy)	• Clinical Phase II (Avastin-Refractory rGBM) • rGBM Phase IIa result presentation at SNO 2020	• Phase II clinical trials of various solid tumors	
Olinvacimab + Pembrolizumab (Keytruda®)	• rGBM Phase Ib abstract at ASCO 2020 (2Q) • Interim result at KSMO 2020 (Sep) • End of Phase Ib: rGBM and mTNBC (3Q) • Phase II a IND submission: mTNBC (4Q) • mTNBC Phase Ib interim result presentation at SABCS 2020 (Dec)	• Phase II (mTNBC)	
PMC-402	• Contracted CDMO with Samsung Biologics • IND enabling studies (4Q)	• Phase I	
PMC-403	• Contracted CDMO with Samsung Biologics • Poster presentation at AACR 2020 (Jun) • R&D cooperation with NIAID for SCLS	• IND enabling studies (2Q)	• Phase I
PMC-309	• A CDMO agreement with Thermo Fisher • IND enabling studies (4Q)	• Phase I	
Others	• GBC2020(Sep)	• JP Morgan Healthcare Conference • AACR 2021 • ASCO 2021	

* SABCS: San Antonio Breast Cancer Symposium

7. Post-IPO

New Team

- **Dr. Hyunsun Park (CBO, COO)**
  ➜ Reinforcement of R&D and business development
- **Distinguished SAB members**
  ➜ Prof. Ferrara and Prof. Cheresh (participated in development of blockbuster drugs such as Avastin)
  ➜ Prof. Soo Hyun Lee (engaged in clinical development at global pharmacetucal companies including Celgene and Pfizer)

Funding

- **Initial Public Offering**
  ➜ Raised U$40m (Nov 2018)
- **Issuance of convertible bonds**
  ➜ Raised U$82m (May 2019)
- The proceeds will be used to fund global clinical developments

R&D

- **New addition to pipeline**
  ➜ PMC-402, PMC-403 and PMC-309
- **Clinical development**
  ➜ Olinvacimab + Keytruda® Phase Ib for rGBM/mTNBC patients in AUS (Jan, 2019)
  ➜ Olinvacimab Phase II for Avastin-refractory rGBM patients in US and AUS (Sept, 2019)

Experience

- **Global Clinical Studies**
  ➜ Currently manages three global trials
- **Collaboration with MSD**
- **Clinical Data Archive**
  ➜ Human data from clinical Studies

8. Benchmarking 1) Public Biotech Companies

We looked at market cap of biotech companies with strong pipeline assets

AnaptysBio

- anti-IL-33, anti-IL-36R (Clinical Phase II)
- Co-Development in IO drug with GSK (PD-1, TIM-3, LAG-3)
- NASDAQ: ANAB

innate pharma
the innate immunity company

- Monalizumab (NKG2A) (Clinical Phase II)
- Co-development in IO drug with AstraZeneca, and Sanofi
- Paris: IPH.PA

Merus

- Bispecific antibody studies (Collaborating with Incyte, and Ono Pharma)
- MCLA-128 (HER2/HER3) in Phase II (Metastatic Breast Cancer)
- NASDAQ: MRUS

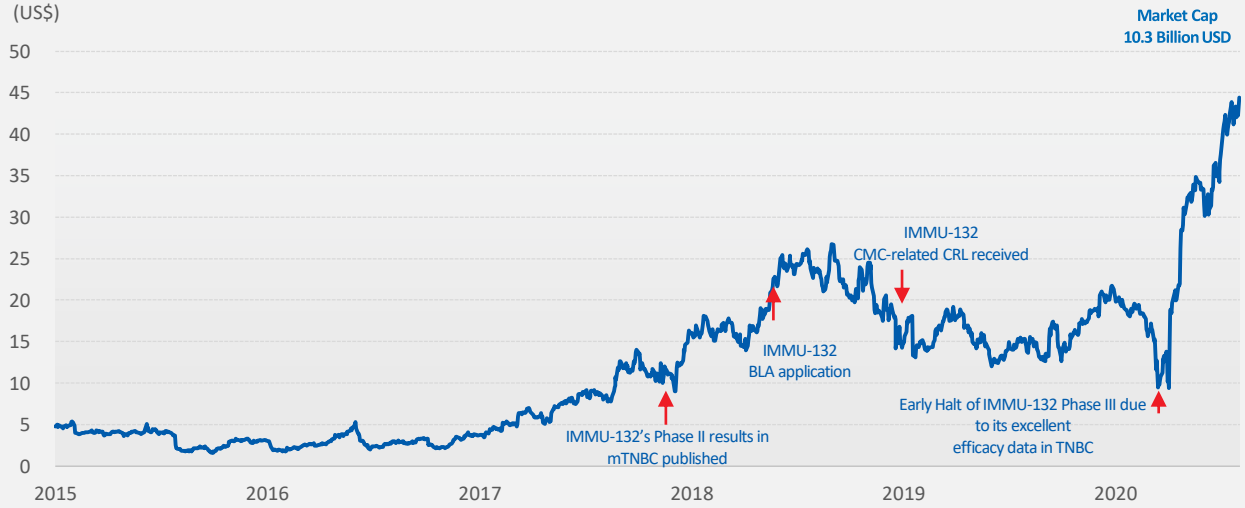
* Market Caps as of Aug.2020

8. Benchmarking 2) Mid-Long Term Goal

The share price performance of Immunomedics is inspiring to us

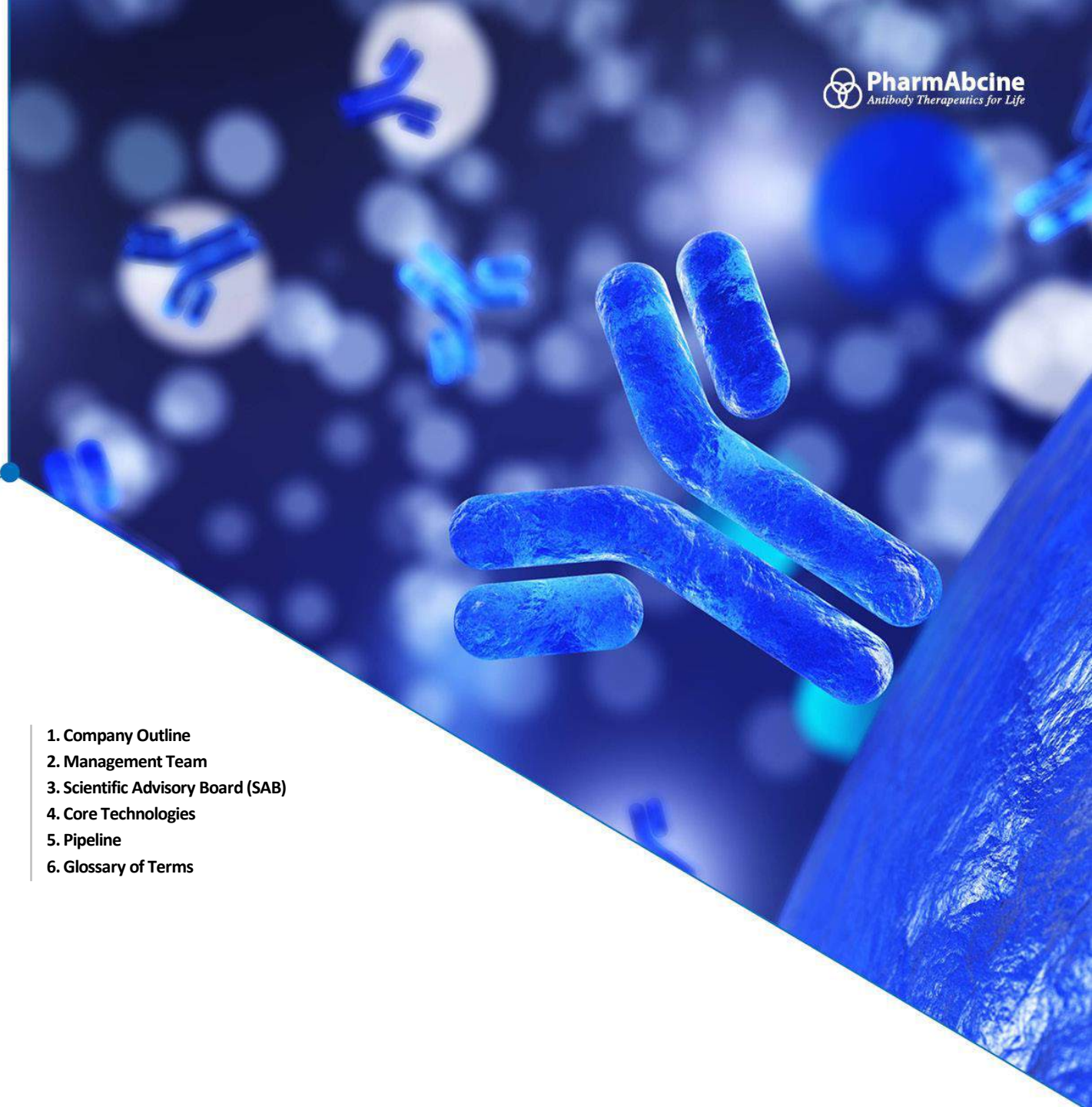
Immunomedics

- Core Pipeline: antibody drug conjugates (ADCs) (i.e. Sacituzumab Govitecan (IMMU-132))
- Conducting mono/combo therapy to develop anti-tumor treatments for a number of indications (Fast Track Designation for mTNBC 3L+)



ANTIBODY
THERAPEUTICS
FOR LIFE

PharmAbcine



Appendix

1. Company Outline

Company Outline

Name	PharmAbcine
CEO	JIN-SAN YOO
Foundation	Sep 3, 2008 (IPO in Nov 21, 2018)
No. of Employee	54 (As of Jun 22, 2020)
Business Area	Antibody and Biologics Therapeutics
Address	• HQ : 2F, Research Building 2, 70, Yuseong-daero 1689 beon-gil, Yuseong-gu, Daejeon, Republic of Korea 34047 • Seoul Branch : IFC 2, 10, Gukjegeumyung-ro, Yeongdeungpo-gu, Seoul, Republic of Korea • Subsidiary in Australia : Level 54,111 Eagle street, Brisbane city QLD 4000 • Subsidiary in U.S (WinCal Biopharm) : 400 Oyster Point Blvd Suite 203 South San Francisco, CA, United States
Awards	• 2008 Grand Prix from 1st GATE Project by Novartis • 2011 Green Technology Certification by MOTIE • 2012 Pharma Idol Award (7th Annual China Pharmaceutical R&D Summit Conference) • 2014 Korea Eureka Day Award by MOTIE • 2014 Tech connect National Innovation Award • 2015 The Best Project of the Year by MSIFP • 2016 Commendation from KFDS • 2017 Commendation from KHIDI • 2018 Biologics Award from KoreaBIO

History & Accomplishments

2008~2013 Foundation

- 2008.09 Foundation of PharmAbcine Inc.
- 2008.10 Grand Prix from 1st GATE Project by Novartis
- 2012.11 Research Collaboration with Sanofi-Aventis
- 2013.03 Out-Licensing of 1E4 mAb

2014~2017 Proof of Competitiveness by Out-Licensing

- 2014.03 Out-Licensing of Olinvacimab (Eye diseases)
- 2014.07 Out-Licensing of PMC-001 (All indications, China/Korea excluded)
- 2014.10 Out-Licensing of Olinvacimab (All indications, China/Korea Only)
- 2016.06 Award from MFDS

2018~ R&D Empowerment by Global Research Collaboration

- 2018.01 Clinical Research Collaboration with MSD for Combo Trials
- 2018.03 ODD Approval of Olinvacimab for GBM from US FDA
- 2018.09 Olinvacimab Phase II IND Approval for Avastin refractory rGBM patients from US FDA
- 2018.11 KOSDAQ IPO

1.1 Company Outline: Accomplishments

- 2008 : Establishment of PharmAbcine Inc
  Grand Prix from 1st GATE Project by Novartis
- 2009 : Series A funding led by Novartis and OrbiMed
- 2011 : Olinvacimab IND approval
- 2013 : Completion of Phase I clinical trial of Olinvacimab
- 2016 : Initiation of Phase IIa clinical trial of Olinvacimab for rGBM patients
- 2017 : Completion of Phase IIa clinical trial of Olinvacimab for rGBM patients in Australia
- 2018 : Listed in KOSDAQ (IPO)
  Initiation of Olinvacimab + Keytruda combo trials (phase 1b) for rGBM and mTNBC patients
- 2019 : Initiation of Phase IIa clinical trial of Olinvacimab monotherapy for bevacizumab refractory rGBM patients

2. Management Team

Jin-San Yoo

President/CEO

- CEO/President, PharmAbcine
- BOD, Chairman
- MAB Expert, EDQM/EU
- Member, Drug Review Committee/KFDS
- Member, Strategic Planning Committee/KFDS
- Adjunct Professor, Chungnam National Univ.
- Director, BioHealthcare Association
- Director, Antibody Society Korea

Hyunsun Park

CBO, COO

- BOD Member
- BA, Seoul National Univ. (1985)
- Ph.D., Stanford University (1987~1993)
- HHMI, Cancer Research Institute postdoctoral fellow, UCLA (1993~1998)
- Sr. Scientist, Essential Therapeutics Inc. CA USA (1999~2003)
- Sr. Scientist, AGY Therapeutics, Inc. CA USA 2003-2005)
- Director, CHDI Foundation & Management , CA USA (2005-2014)
- CEO, Naason Science USA & Korea (2016-2018)
- CSO, BioLeaders Corp. Korea (2018-2019)

Weon Sup Lee

Head of R&D Center

- BOD Member
- Ph.D., KAIST (2004)
- Post-Doc. SUNY (2004~2006)
- Post-Doc. KRIBB (2006~2008)
- PharmAbcine (2008~Present)
- PI of the Best Project of the Year (2015)
- Commendation from MSIFP(2015)

TaeWon Lee

CSO (WinCal)

- Founder of Wincal Biopharm
- Ph.D., University of Glasgow
- Post-Doc. Stanford
- Program Leader, Amgen
- Research Scientist, Theravance Biopharma

2. Management Team

Jun Hee Choi CGAO

- BOD Member
- BS, Seoul National Univ. (1989)
- KEPCO (1989~1995)
- Legal Dept., POSCO E&C (1996~2015)
- CEO, GIK (2015~2016)
- Oversea Legal Dept., POSCO E&C (2016~2019)

Du Yung Jung Auditing Director

- BS, HANKUK UNIVERSITY OF FOREIGN STUDIES (1982)
- MBA, Pennsylvania Univ. Wharton School (1995)
- Int. Finance, Hyundai Financial (1984~1999)
- Investment & Finance, Johong Bank (1999~2006)
- Business Development, Shinhan Bank (2006~2016)

Paul Chulbum Kim CFO

- BOD Member
- BS, New York University Stern School (1987)
- MBA, Rutgers University GSM (1990)
- KPMG LLC (1992-1997)
- BNP Paribas (2001-2005)
- Allianz Global Investors (2005-2007)
- KB Securities Co., Ltd (2009-2014)

Dong Seup Lee M.D

- BOD Member
- Ph.D, Seoul University
- Immunology, Cancer Biology Laboratory
- Anatomy, Cell Biology, Med. Seoul University
- Cancer Research Cent., Organ Transplant Research Cent., Genetic Research Cent., Seoul University

Hyun Suh Gu Patent Attorney

- BOD Member
- KEY IP&Law Firm Rep. Patent Attorney
- IP Dossier Rep. Patent Attorney
- Korea Health Industry Development Institute Chief Attorney
- Experience in Pharmaceutical Patents with Daewoong, Green Cross, Hyundai Pharm.

3. Scientific Advisory Board (SAB)

Napoleone Ferrara

UC San Diego Moores Cancer Ctr.

- Senior Deputy Director for Basic Science
- Distinguished Professor of Pathology at UCSD School of Medicine
- Distinguished Adjunct Professor of Ophthalmology and Pharmacology at UCSD
- Inventor of Avastin® and Lucentis®
- Pioneer of the Angiogenesis Therapy in Oncology and Ophthalmology

David Cheresh

UC San Diego Moores Cancer Ctr.

- Distinguished Professor and Vice Chair of Research at Pathology Dept.
- Director for Translational Research at UCSD Moores Cancer Ctr.
- Inventor of Unituxin® and Vitaxin®
- Outstanding Investigator Award from NCI
- MERIT Award from both NIH and NCI

Dong Moon Shin

Winship Cancer Institute

- Vice President at Winship Cancer Institute
- Distinguished Professor at Emory Univ.
- Adjunct Professor at Georgia Tech.
- PI of Winship Cancer Institute Chemoprevention Program
- Best Doctors in America (2003~2014)

Do Hyun Nam

Samsung Medical Ctr.

- Chairman of SMCIRCR
- Professor at Sung Kyun Kwan Univ.
- PI at Cancer Stem Cell Research Ctr. at SMC
- QA Clinic Ctr. at SMC
- Seoul National Univ. School of Medicine (MD/Ph.D)

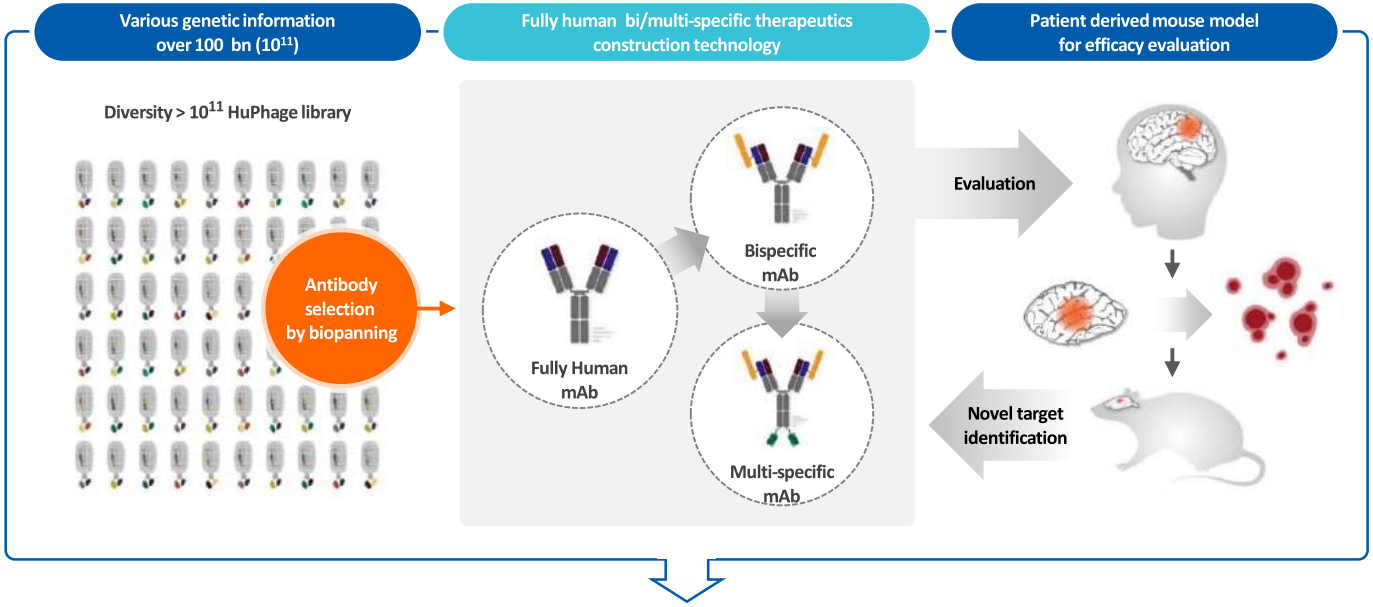
Soo Hyun Lee

Korea Univ. Medical Ctr.

- Professor, Division of Hemato-Oncology at KUMC
- Country Medical Director at Celgene
- Korea Oncology Medical Lead at Pfizer
- Medical Oncologist at Severance Medical Center

4. Core Technologies 1) Platform Technology for Antibody Drugs

A proprietary platform technology to develop fully human antibody therapeutics
enabling discovery to generation of bi-/multi-specific antibody



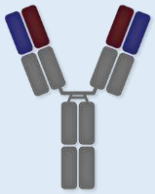
Platform technology for bi/multi-specific therapeutics development

4. Core Technologies 2) Bi- and Multi-specific Antibody Therapeutics

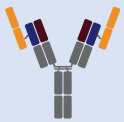
Technologies to build versatile bi-/multi-specific antibody therapeutics

Fully Human Antibody

PharmAbcine
Antibody Therapeutics for Life



Bi-specific DIG-body™

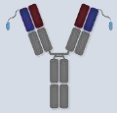


2nd target (Domain)

IgG + Domain

- PMC-001, PMC-002R, PMC-122, PMC-202 etc.

Bi-specific PIG-body™

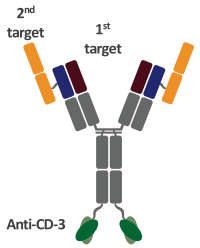


2nd Target (peptide)

IgG + Peptide

- Alternative way to solve low PK issue of peptide therapeutics
- PIG-KM etc.

Multi-specific TIG-body



IgG + Domain / Peptide + T cell engager

Enhancement of anti-cancer activities by T-cell immunity in addition to bi-specific antibody

Patents Relate to Bi-/Multi-specific Antibody

1. Registration in domestic/oversea 28 cases
2. Pending Application 3 cases

5. Pipeline 1) Olinvacimab (TTAC-0001, Clinical)

Best-in-class candidate with impressive safety profile compared to competitive drugs

Pipeline Introduction : Mono Therapy

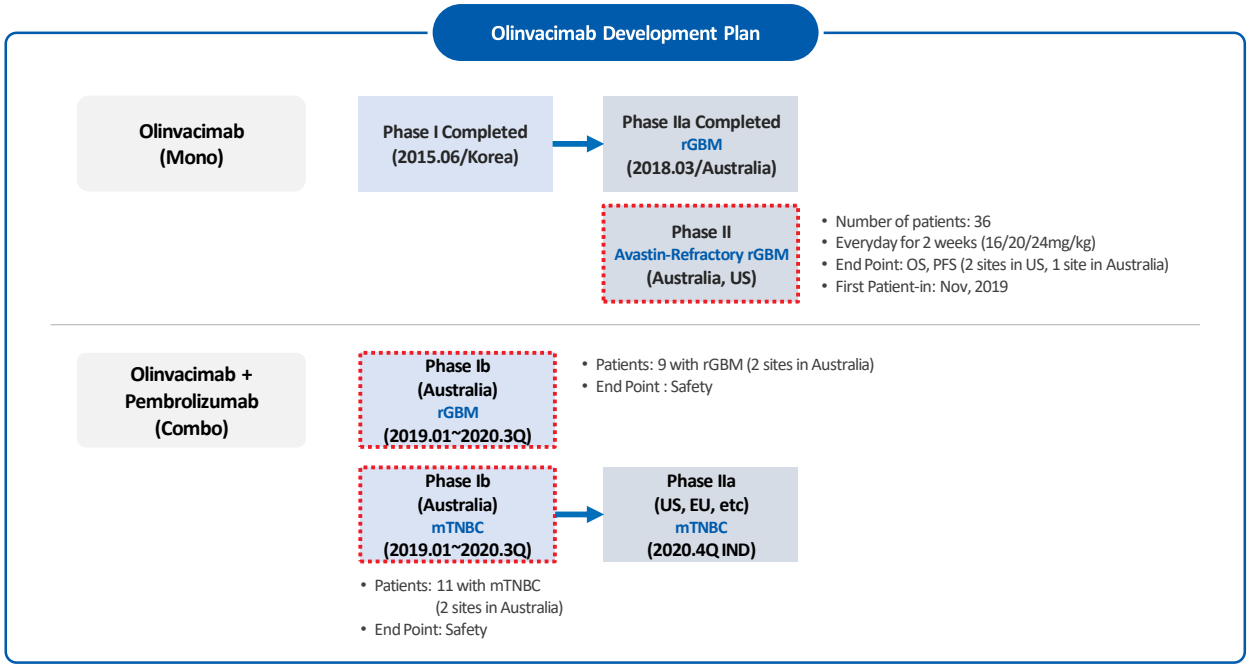
MOA	• anti-VEGFR2 》 Regulates the Growth of Tumor Angiogenesis
Indications	• rGBM, **Avastin-refractory rGBM** • Ocular Diseases: AMD, DR, etc
Competitors	• Cyramza[ramucirumab] (Identical MOA), Avastin[bevacizumab], Zaltrap/Eylea[Aflibercept], Lucentis[Ranibizumab] (Similar MOA) are already marketed and other molecules are in clinical stage
Competitiveness • Development Strategy	• Unmet medical needs arising from drug-resistant tumors • The ONLY VEGFR2-targeting Antibody drug with species cross-reactivity for human and mouse: Results from mouse studies can be translated to human

Pipeline Introduction : Combo Therapy

MOA	• anti-VEGFR2 + anti-PD1 》 Regulates the growth of tumor angiogenesis + T cell activation through immune checkpoint inhibition
Indications	• rGBM, **mTNBC**, currently planning to expand its therapeutic uses in other indications
Competitiveness • Development Strategy	• Based on the results from clinical trial phase Ib, we will initiate a phase IIa combo clinical trial on mTNBC in collaboration with MSD early next year • Focusing on mTNBC combo trial with pembrolizumab (Keytruda®) • Reviewing different combo therapy options with small molecules

5. Pipeline 1) Olinvacimab (TTAC-0001, Clinical)

Focusing on combo therapy with Pembrolizumab (Keytruda®) in mTNBC clinical trial



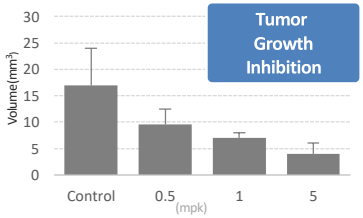
5. Pipeline 1) Olinvacimab (TTAC-0001, Clinical)

Excellent safety and efficacy profile comparing to other drugs

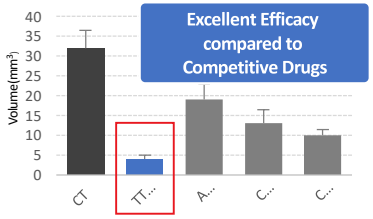
"Best-in-Class"

Preclinical Result

Tumor Growth Inhibition in GBM Mouse Model



Olinvacimab VS. Competitive Drugs

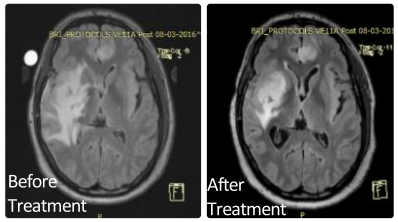


Phase I Result

Excellent Safety Profile

- No DLT observed at 24mg/kg
  → Possible to apply for childhood cancer patients who are not drug-tolerable enough
- Increase of specific biomarkers (VEGF-A, sVEGFR2, PIGF) in serum
- Shown 60% SD (Stable Disease)
- Not shown common side effects in competitive drugs like hypertension, bleeding, gastric/lung perforation, proteinuria etc.

Phase IIa Result



- 25% Disease Control Rate(DCR) (Max. 16 Mo)
- Edema relief in 42% patients
- Tumor reduction in 25% patients
- Steroid use reduction in 17%
- Survival at Max. 525 days

Approval of ODD for rGBM from US FDA
Clinical Trials With MSD's Keytruda®

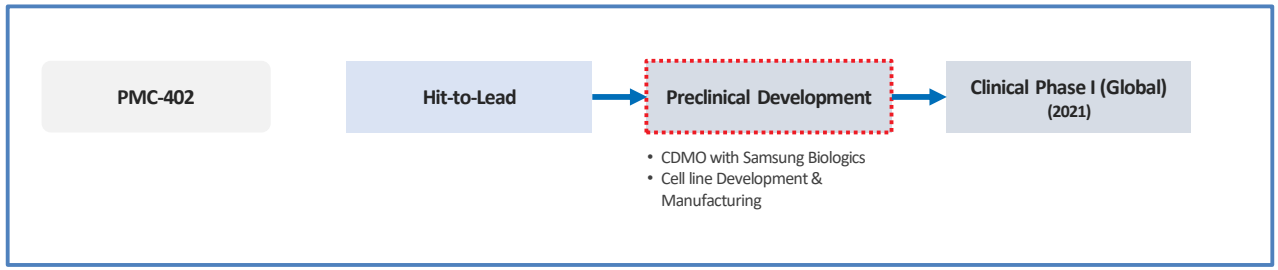
5. Pipeline 2) PMC-402 (Preclinical)

First-in-class Tie2-activating vessel normalizer

Pipeline Introduction

MOA	• Tie2 activator 》 vessel normalizer, Increased T cell infiltration
Indications	• Solid tumors (Combo with IO drugs)
Competitors	• TIE2-activating biologics are all in preclinical stage • AKB-9778 from AERPIO is a clinical stage small molecule targeting VE-PTP (VE-PTP inhibition leads to activation of TIE2)
Competitiveness • Development Strategy	• Monoclonal antibody: easy manufacturing and higher safety profile • Overcoming limitations of existing angiogenesis inhibitors through vessel normalization • Ligand-independent (Ang1/Ang2)

Pipeline Development Plan



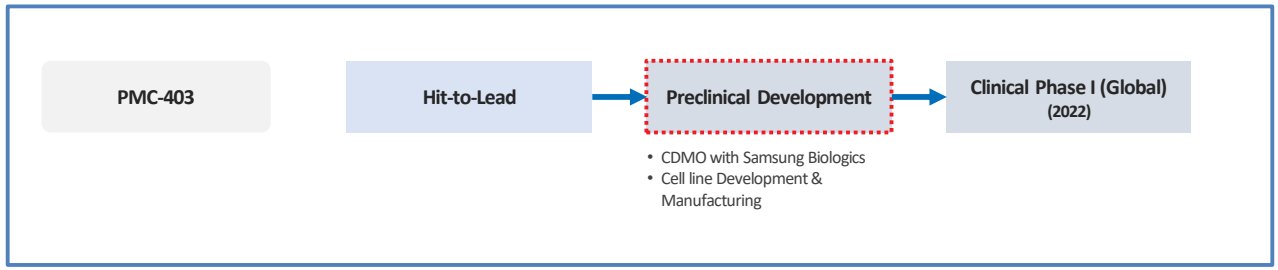
5. Pipeline 3) PMC-403 (Preclinical)

First-in-class Tie2-activating vessel normalizer

Pipeline Introduction

MOA	• Tie2 activator 》 vessel normalizer
Indications	• Ocular Diseases (AMD and DR) • ARDS(Acute respiratory Distress Syndrome) • AKI(Acute Kidney Injury)
Competitors	• TIE2-activating biologics are all in preclinical stage • AKB-9778 from AERPIO is a clinical stage small molecule targeting VE-PTP (VE-PTP inhibition leads to activation of TIE2)
Competitiveness• Development Strategy	• Monoclonal antibody: easy manufacturing and higher safety profile • Overcoming limitations of existing angiogenesis inhibitors through vessel normalization • Ligand-independent (Ang1/Ang2)

Pipeline Development Plan



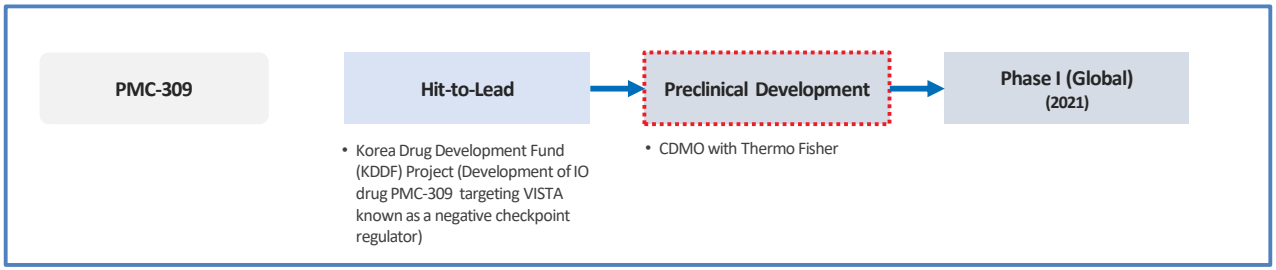
5. Pipeline 4) PMC-309 (Preclinical)

First-in-class anti-VISTA mAb

Pipeline Introduction

MOA	• anti-VISTA 》 Restoration of anti-tumor effects of T cells by targeting VISTA expressed on MDSCs (Myeloid Derived Suppressor Cells) in TME
Indications	• Solid tumors
Competitors	• Global biotech companies are developing anti-VISTA mAbs • Boehringer Ingelheim, Pierre Fabre, Curis, Hummingbird Bioscience, and Xcella Biosciences are in preclinical stage
Competitiveness • Development Strategy	• Since PMC-309 specifically targets VISTA expressed on MDSCs, its anti-tumor effect can be observed in monotherapy and synergistic, enhanced anti-tumor effect can be observed in combination therapy • In humanized mouse model bearing TNBC, PMC-309 showed its excellent anti-tumor effect and suitability for combination therapy

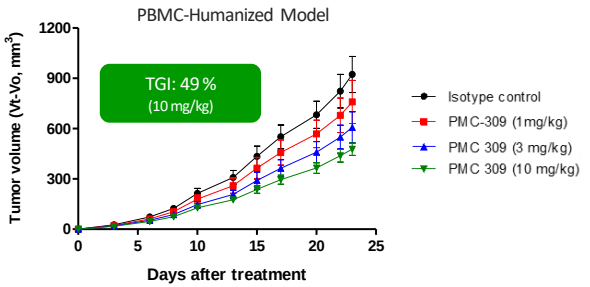
Pipeline Development Plan



5. Pipeline 4) PMC-309 (Preclinical)

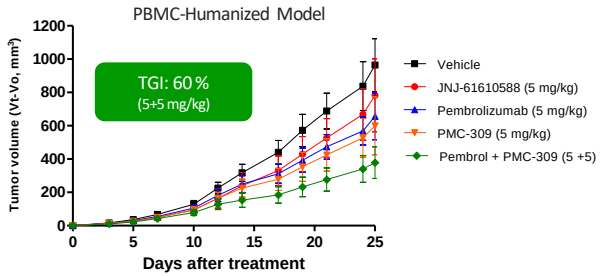
Excellent efficacy and potential synergy with anti-PD-1 antibody in an mTNBC model

Preclinical Result



Dose-dependent anti-tumor effect

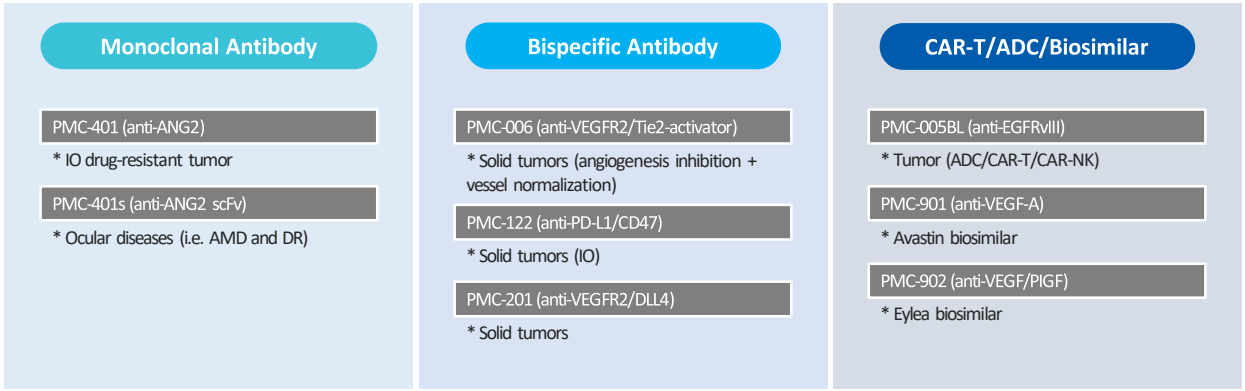
Preclinical Result



Enhanced TGI with anti-PD1 mAb
▼
Pembrolizumab combination

* TGI: Tumor Growth Inhibition

5. Pipeline 5) Early R&D Project



6. Glossary of Terms

Terms	Definition
ARDS (acute respiratory distress syndrome)	A type of respiratory failure characterized by rapid onset of widespread inflammation in the lungs. Mechanism involves diffuse injury to cells which form the barrier of the microscopic air sacs of the lungs, surfactant dysfunction, activation of the immune system, and dysfunction of the body's regulation of blood clotting.
Library	A collection of DNA fragments that is stored and propagated in a population of micro-organisms through the process of molecular cloning. Mainly used for HTS screening. Usually contains information on structure, purity, quantity and characteristics of compounds.
Combination therapy	A therapy that uses more than one medication or modality to improve therapeutic effects.
Receptor	Chemical structures, composed of protein, that receive and transduce signals that may be integrated into biological systems. Signal, once sent onward, amplification increases the effect of a single ligand, and integration allows the signal to be incorporated into another biochemical pathway.
Bispecific antibody	An artificial protein that can simultaneously bind to two different types of antigen. It can be manufactured in several structural formats, and current applications have been explored for cancer immunotherapy and drug delivery.
Mode of Action (MOA)	Describes a functional or anatomical change, resulting from the exposure of a living organism to a substance.
Indication	Disease or symptoms showing therapeutic effects from medication or medical procedure.
Targeted therapy	Therapy made for the purpose of targeting particles from tumor cells to show therapeutic effects.
Antigen	A molecule or molecular structure, such as may be present at the outside of a pathogen, that can be bound to by an antigen-specific antibody (Ab) or B cell antigen receptor (BCR). The presence of antigens in the body normally triggers an immune response.
Antibody	A large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to neutralize pathogens such as pathogenic bacteria and viruses.
Antibody therapeutics	Therapeutics made with antibodies showing high infinity to antigens living organism. A type of Bio-medicine that shows therapeutic effects by conjoining with protein secreted from/in cellular wall.
Orphan Drug Designation	A pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance.
scFv	A single-chain variable fragment (scFv) is a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a short linker peptide of ten to about 25 amino acids. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker.
Phage	A virus that infects and replicates within bacteria and archaea. Virus cannot self replicate, meaning it infects to bacteria and replicates itself using bacteria's self replication system.
IgG	A type of antibody. Representing approximately 75% of serum antibodies in humans, IgG is the most common type of antibody found in blood circulation.

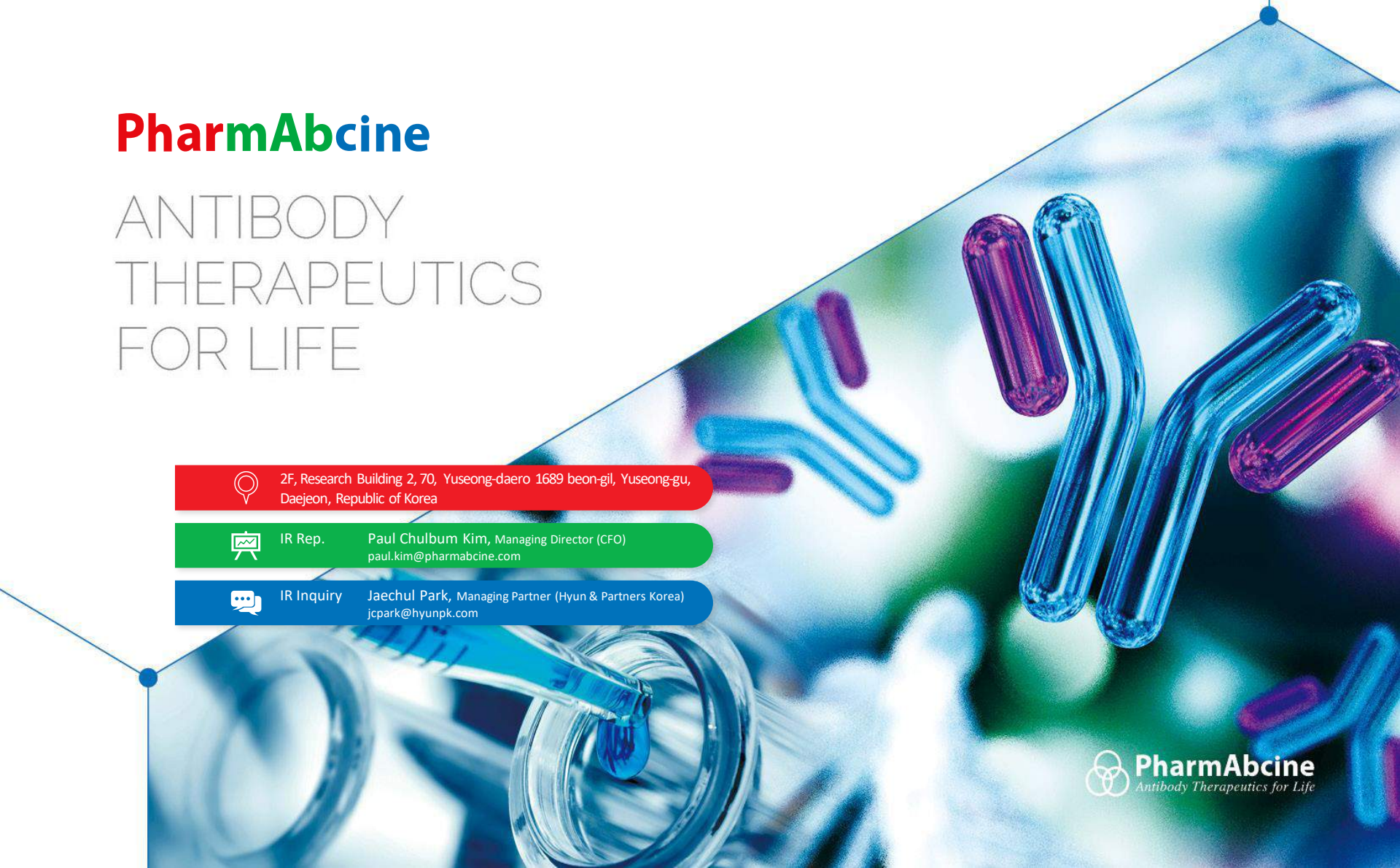
PharmAbcine

ANTIBODY THERAPEUTICS FOR LIFE

2F, Research Building 2, 70, Yuseong-daero 1689 beon-gil, Yuseong-gu, Daejeon, Republic of Korea

IR Rep. Paul Chulbum Kim, Managing Director (CFO)
paul.kim@pharmabcine.com

IR Inquiry Jaechul Park, Managing Partner (Hyun & Partners Korea)
jcpark@hyunpk.com



Strategic Planning in Global Clinical Development

지 동 현

Sep. 25, 2020

BIOPLUS INTERPHEX KOREA

Table of Contents

Global Development

Global Development Considerations

- Generation of data that enable simultaneous approvals in major markets (e.g., US, Europe, Japan & China).
  - Develop meeting internationally accepted ethic and scientific standards.
  - Consider potential ethnic sensitivity.
  - Consider different regulatory requirements in different countries or regions for market authorization.
  - Need a well-thought global clinical development strategy and a plan to minimize the development time and cost.
  - Need a clinical study design incorporating different medical practice and SOC.

Clinical Development Plan (CDP)

What Is a Clinical Development Strategic Plan (CDP)?

- A carefully planned set of clinical trials.
- From FIH Phase 1 to P2 POC and pivotal P3 trials
- Design trials sufficient for both regulatory approval and market success.
- Design trials to provide data for making investment and/ or partnering decisions during development.
- Start from your TPP.

Selection of Drugs to Enter Exploratory Development

- High unmet medical need
  - Current treatment (SOC) for target condition in the target markets
- Well understood mechanism of action (MOA)
- Proposed proof of concept (PoC) study is feasible.
  - Efficacy clues with intended doses, regimens, a route of administration and disease models.

Strategic Planning Approach - How TPP Fits In

Preparation to Begin A CDP

- Physician-scientists first review the preclinical profile of the new drug candidate (e.g., its pharmacology, mechanism of action and toxicology)
- Summarize their assessment on the impact to clinical trial design, as well as proposed therapeutic use in patients.
- The medical and scientific rationale for the drug product to ensure market acceptance by healthcare providers, patients and professional medical organizations.

Questions To Be Asked

CLINICAL	BUSINESS
• Patients • Comparators • Endpoints • Future Landscape • Value creation in biopharma • Lifecycle strategy	• Stakeholders • Launch strategy • Positioning • Market Drivers • $ • Value creation in biopharma • Lifecycle strategy

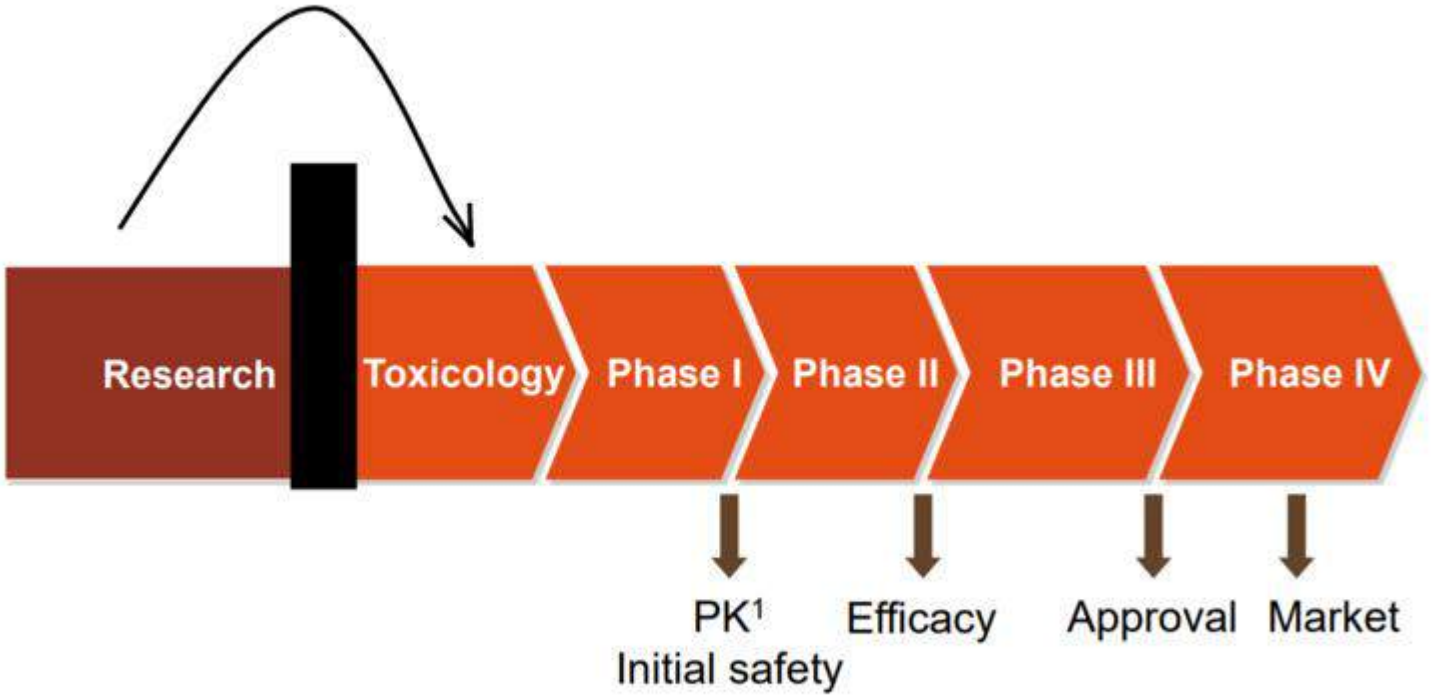
A Strategic CDP: To Enhance the Product Benefit Risk Profile

An Example of An Early Phase CDP

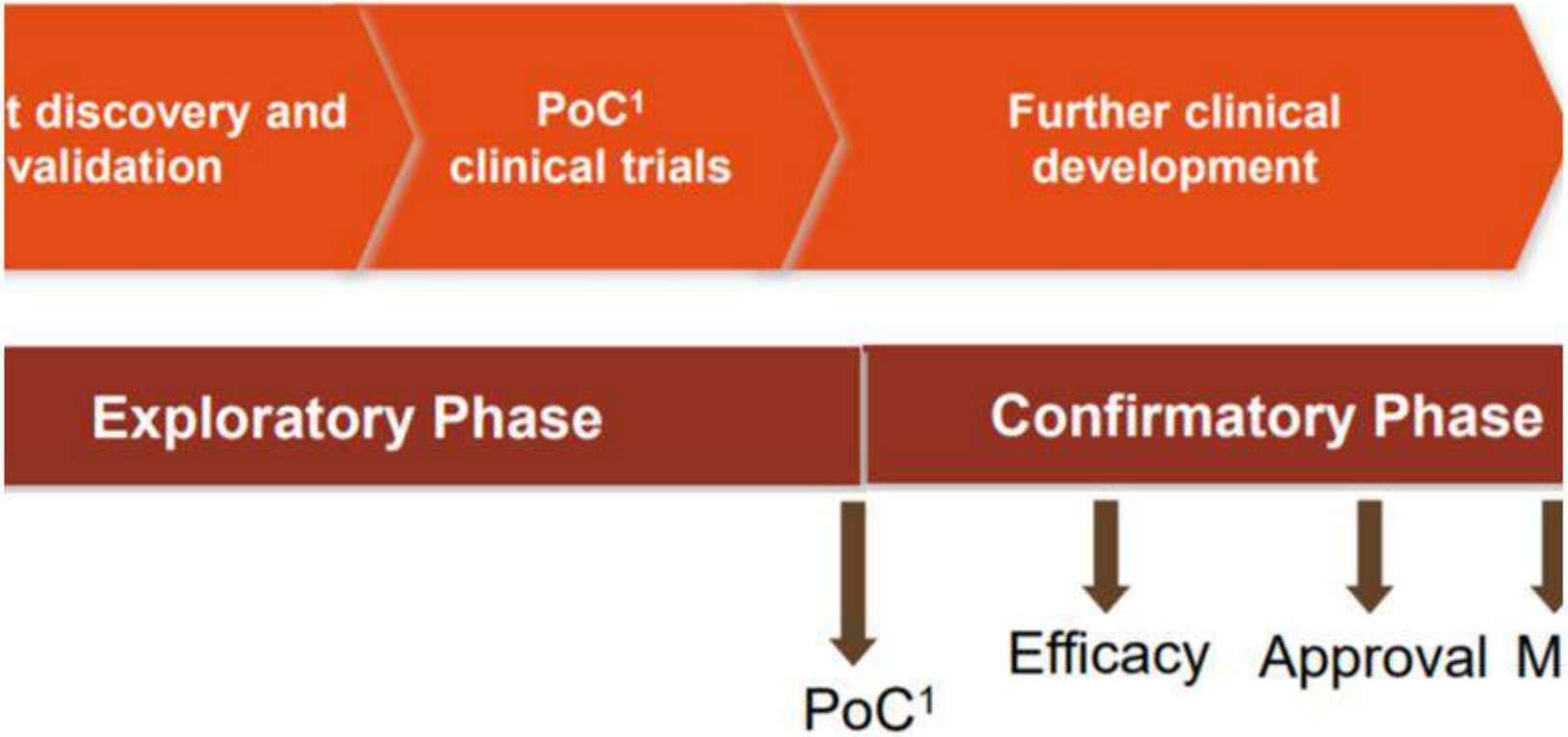
Phase 1 (early phase trial) for global development

- Ethnic bridging to enhance asset value and accelerating Global drug development. (ICH E5)
  - Multiethnic group phase 1 study
  - Proof of being less likely to be ethnically sensitive.
- Novel approaches in the design of clinical trials to rapidly expedite the access of potentially life-saving therapies to patients while assuring safety and efficacy to support earlier POC.

Old Paradigm of Drug Development



New Paradigm (Novartis)

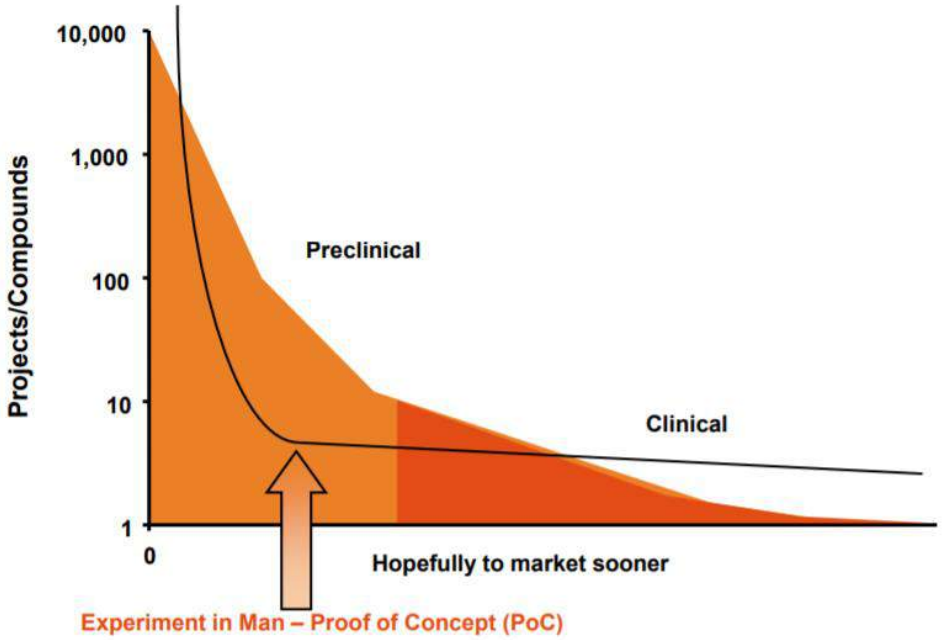


- Combine elements of traditional Phase I/II testing
- typically involving in the range of between five and 15 patients

- Has elements of traditional Phase II/III testing and includes trials aimed at confirming the safety and efficacy in the given indication.

PoC Study conduct

- Confirm patho-biology pathway in human.
- Typically small and short
- Single open vs. RCT
- Biomarker: drive Go/No-Go decision
- Most studies have adaptive features, some are heavily adaptive.
- Many are multicenter, multinational



False positive result is “the worst sin”

Adopted from Robert Schmouder, ASCPT 2012

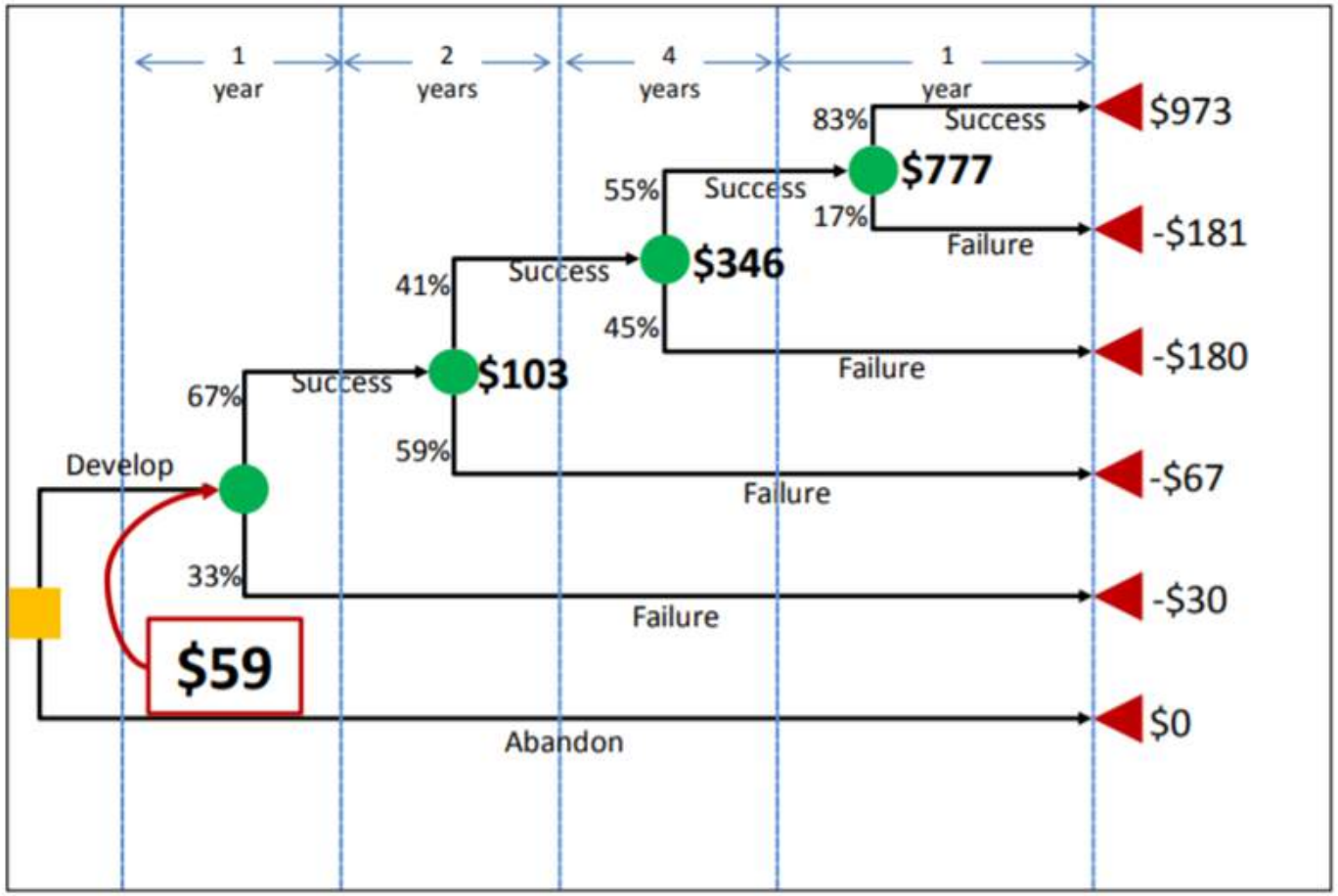
Global Clinical Trial Planning and Barriers

Cost Considerations

- Decision process from the point of view of an expected-revenue-maximizing sponsor in the face of uncertainty (or risk) with following considerations:
  - Therapeutic area,
  - Potential market size/revenues for the drug, and
  - Clinical stage (Phase 1, Phase 2, Phase 3, and Phase 4) costs that are dependent on a variety of factors, including but not limited to:
    - Physician and RN costs;
    - Number of patients needed for the desired statistical precision;
    - Number of IRBs involved;
    - Number of investigator sites;
    - Cost of clinical data collection, management, and analysis; and
    - Cost of clinical procedures

Start from 'Value and Risk'

- Drug Development Decision Tree Depicting Net Present Value (NPV) of Returns at Each Node



Clinical Trial Cost 1

- Per-study costs is the sum of:
  - Data collection, management and analysis costs (per study)
  - Cost per Institutional Review Board (IRB) approval × Number of IRB approvals (pe study)
  - Cost per IRB amendment × Number of IRB amendments (per study)
  - SDV Cost (per data field) × Number of SDV fields (per study), and
  - The total of all per-site costs listed below, multiplied by Number of Sites (per study)

Clinical Trial Cost 2

- Per-site costs is the sum of:

  The total of all per-patient costs listed below, multiplied by Number of Planned Patients (per site)

  - Site Recruitment Costs (per site)
  - Site Retention Costs (per month) × Number of Site Management Months
  - Administrative Staff Costs (per month) × Number of Project Management Months, and
  - Site Monitoring Costs (per day) × Number of Site Monitoring Days

Clinical Trial Cost 3

- Per-patient costs is the sum of:
  - Patient Recruitment Costs (per patient)
  - Patient Retention Costs (per patient)
  - Registered Nurse (RN)/Clinical Research Associate (CRA) Costs (per patient)
  - Physician Costs (per patient)
  - Clinical Procedure Total (per patient), and
  - Central Lab Costs (per patient)

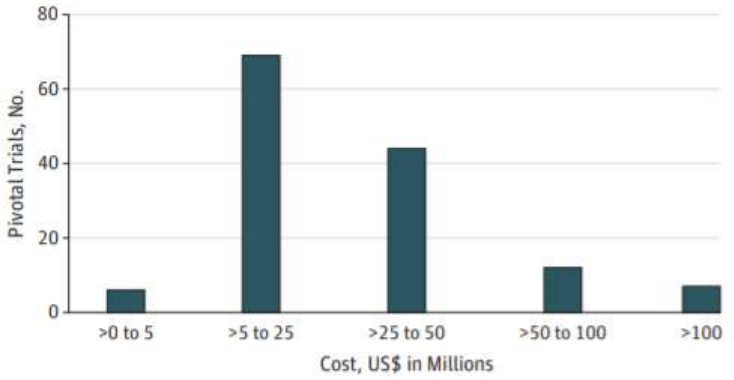
Clinical Trial Cost by Phase

Table 1. Characteristics of Novel Therapeutic Agents Approved From 2015 to 2016

Characteristic	No. (%)
Total therapeutic agents	59 (100)
Expedited approval pathway[a]	
Accelerated approval	12 (20.3)
Breakthrough	17 (28.8)
Fast track	21 (35.6)
Priority review	35 (59.3)
None	21 (35.6)
Incentive	
Orphan drug	27 (45.8)
Molecule type	
Biologic	18 (30.5)
Small molecule	41 (69.5)
Pivotal clinical trials per therapeutic agent	
1	27 (45.8)
2	14 (23.7)
3	7 (11.9)
4	6 (10.2)
≥5	5 (8.5)

[a] Therapeutic agents could qualify for multiple approval pathways.

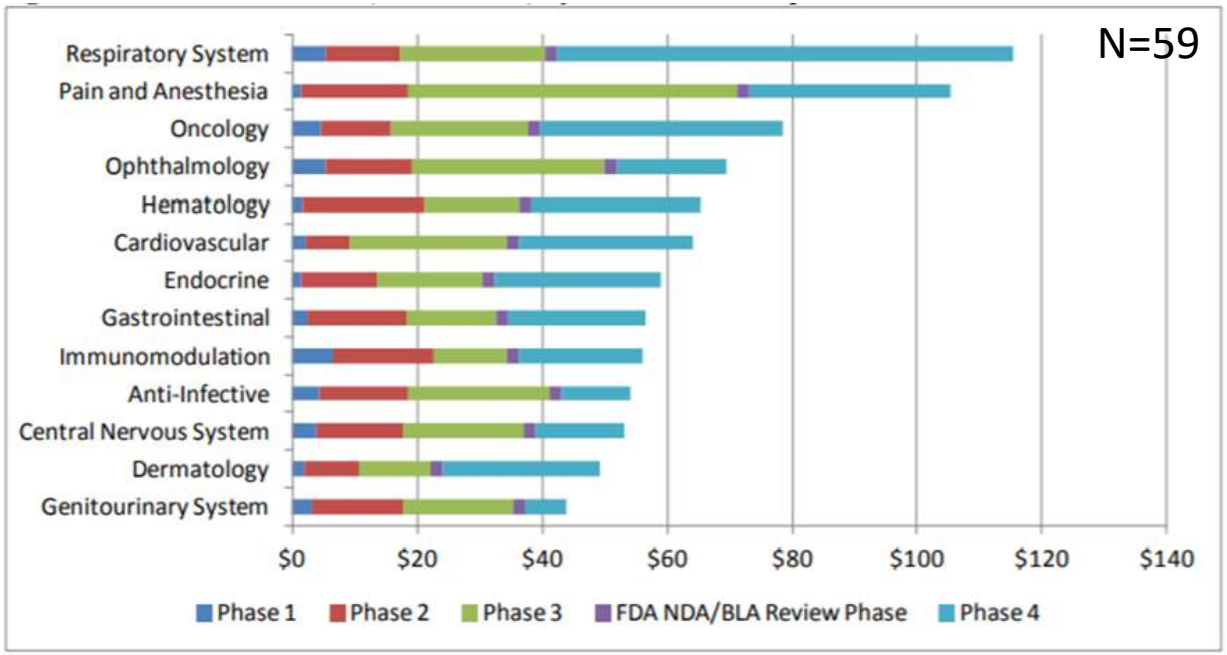
Figure. Pivotal Trial Cost Estimates of Novel Therapeutic Agents Approved by the US Food and Drug Administration From 2015 to 2016



- As general rule of thumb, the average cost of phase 1, 2, and 3 clinical trials across therapeutic areas is $4, 13, and 20 million respectively.
- Pivotal studies cost a median of $41,117 per patients.

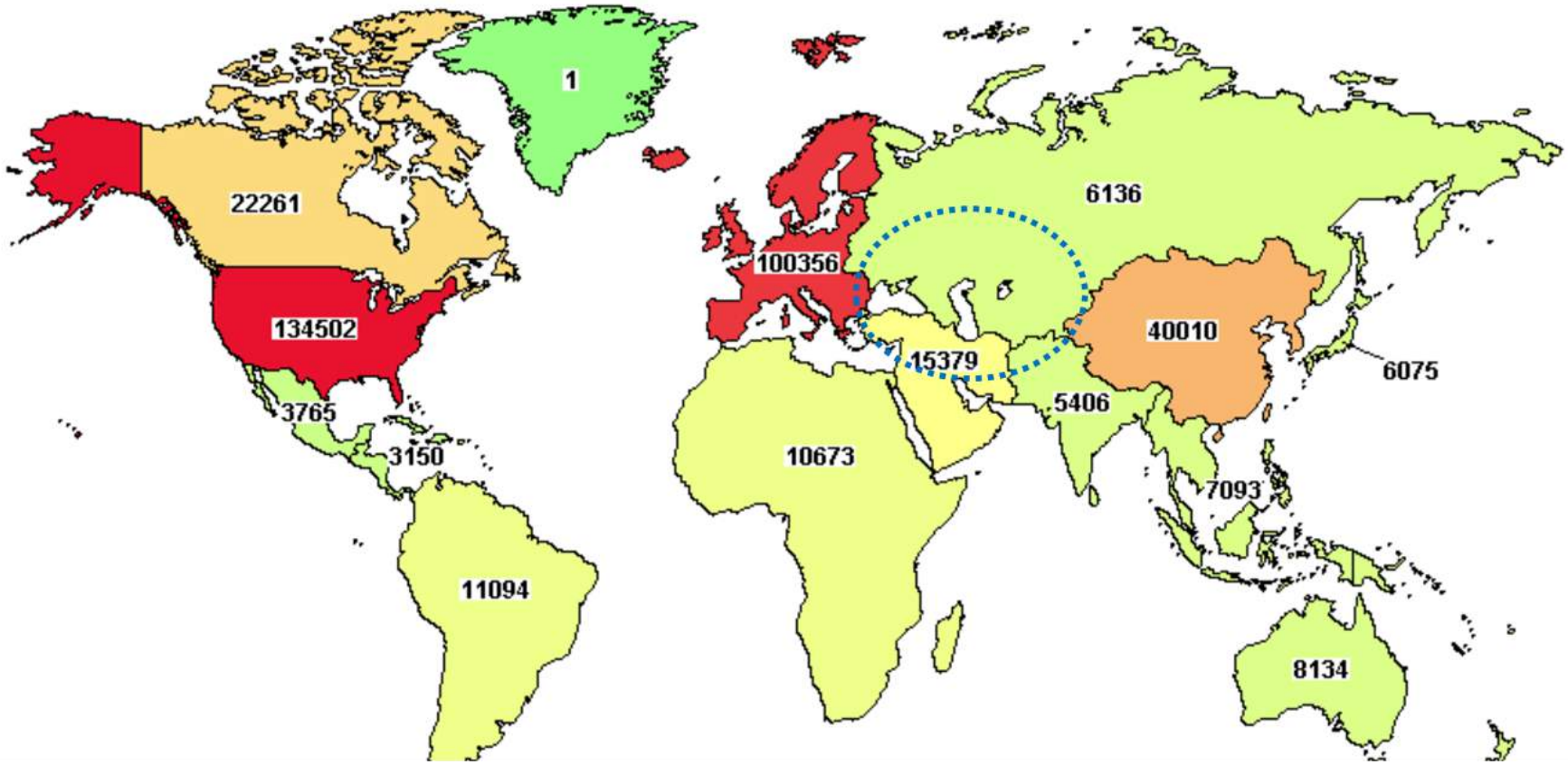
https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development
JAMA Intern Med. 2018;178(11):1451-1457

Cost by TA

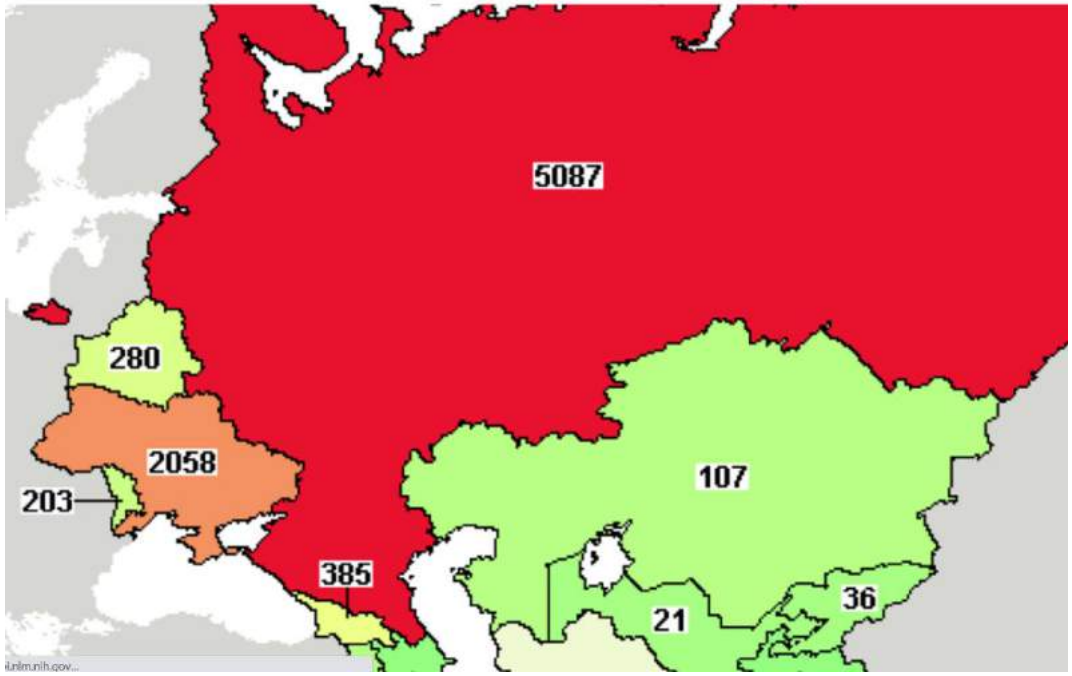


- 59 new therapeutic agents approved by the FDA from 2015 to 2016, the median estimated direct cost of pivotal efficacy trials was $19 million, with half of the trial cost estimates ranging from $12 million to $33 million.
- At the extremes of the distribution were 100-fold cost differences, and patient enrollment varied from fewer than 15 patients to more than 8000 patients.

Where to Go?


1
22261
134502
3765
3150
11094
100356
6136
40010
15379
5406
6075
10673
7093
8134
Colors indicate the number of studies with locations in that region.
Least
Most
Labels give the exact number of studies.

Where to Go II



- Recruitment Feasibility
  - Naïve vs. experienced patients
  - Similar SOC

- Regulatory process and speed
- GCP compliance
- Cost
- CROs with track records.
- Experienced investigators with track records.

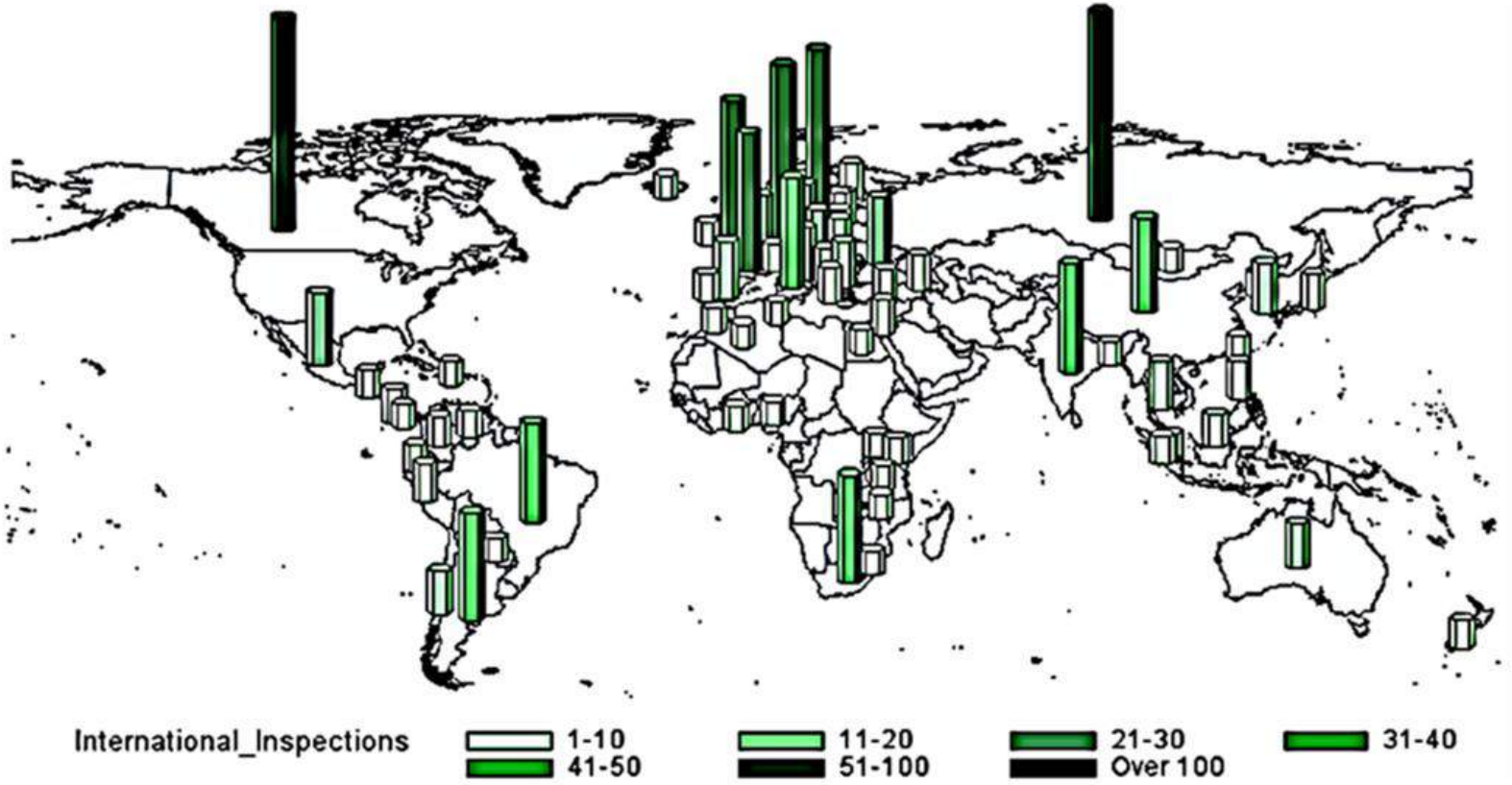
FDA Accepts Foreign CTs?

Useful Guidance

- FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions
  - Issued March 2012
  - Provides clarifications for sponsors and applicants on how to demonstrate compliance with the requirements of 21 CFR 312.120

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

Global Coverage of GCP Inspections

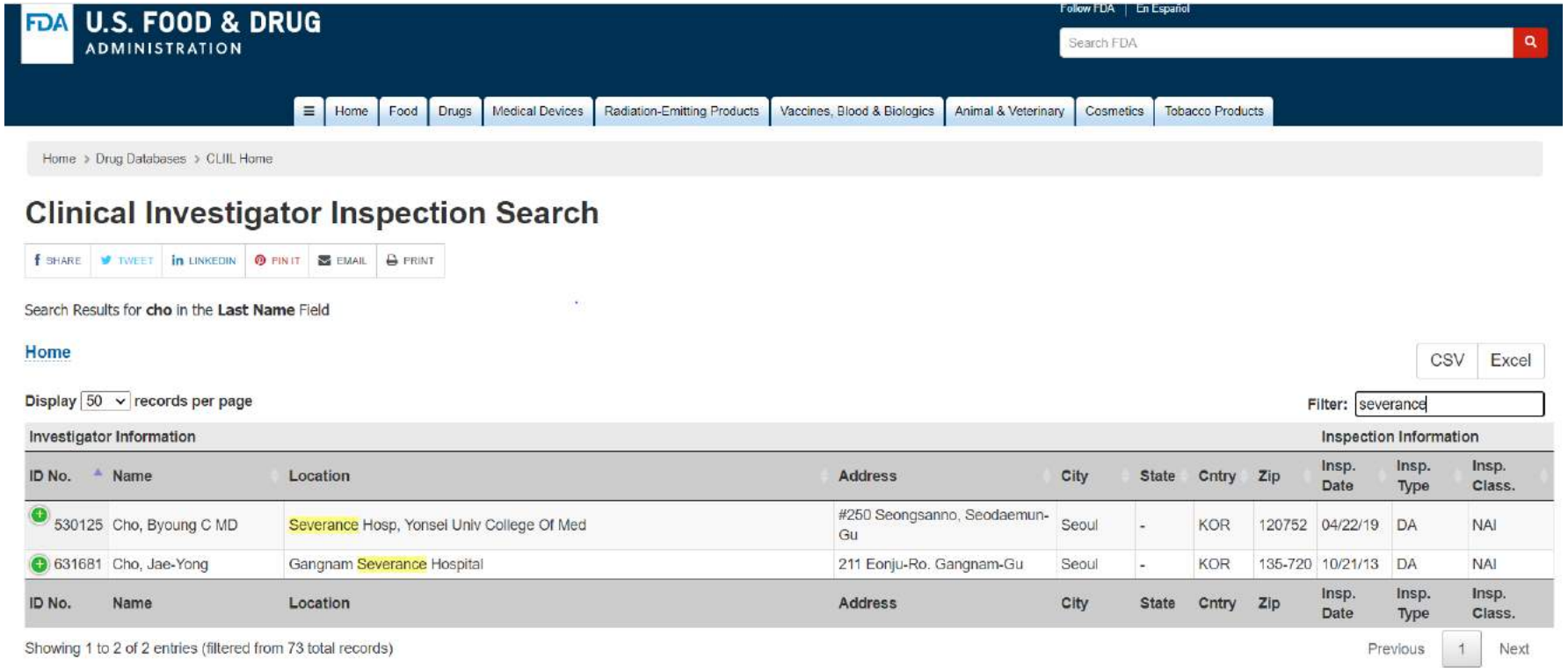


Conducted for FDA/CDER from 1984 through Sept 3, 2013; Based on Inspections with a start date in CDER/OC/OSI database

What must be submitted to FDA?

1. CI's qualifications
2. Description of the research facilities
3. Summary of the protocol & results of the study &, should FDA requ est, case records
4. Description & details of the product/drug used
5. Information showing that the study is adequate & well controlled.
7. Name & address of the IEC, a summary of the IEC's decision
8. A description:
    - how IC was obtained
    - what incentives, if any, were provided to subjects in the study
    - how the sponsor(s) monitored the study
    - how CIs were trained to comply with GCP

Kassa Ayalew, FDA



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Investigator Information								Inspection Information		
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530125	Cho, Byoung C MD	Severance Hosp, Yonsei Univ College Of Med	#250 Seongsanno, Seodaemun-Gu	Seoul	-	KOR	120752	04/22/19	DA	NAI
631681	Cho, Jae-Yong	Gangnam Severance Hospital	211 Eonju-Ro. Gangnam-Gu	Seoul	-	KOR	135-720	10/21/13	DA	NAI
ID No.	Name	Location	Address	City	State	Cntry	Zip	Insp. Date	Insp. Type	Insp. Class.

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August 2020

More Information on Search Form Fields

Complete Inspection Classification Dataset

Classification

All
NAI - No Action Indicated
VAI - Voluntary Action Indicated
OAI - Official Action Indicated

Project Area

Project 41 - Human Cellular, Tissue, and Gene Therapies
Project 42 - Blood and Blood Products
Project 45 - Vaccines and Allergenic Products
Center for Drug Evaluation and Research
Project 48 - Bioresearch Monitoring
Project 53 - Postmarket Surv. and Epidemiology

Firm Name

Country / Area

Russia

Other Barriers for Multi-site Trials

- Great deal of complexity to the process of conducting clinical trials
  - The abundance of regulations at various levels
  - Lack of harmonization
- Reporting of results, format for applications, guidance on endpoints, registration requirements, guidelines for clinical programs, biosimilars legislation, and adverse events reporting, financial disclosure thresholds.
- Lack of clear Regulatory Pathways and Guidance for Some Therapeutic Areas.
- Sponsor-imposed barriers (legal, conservative assumptions, contract internal review, etc.).
- Study design (eligibility, complex protocol, failure to integrate study design with clinical practice , etc.).

Thank you for your attention!