BIOPLUS INTERPHEX KOREA

Cenobamate FDA 신약개발

정구민

24th September, 2020

SK biopharmaceuticals

Table of Contents

I. SK바이오팜

- ✓ 성장 연혁 및 자회사 현황
- ✓ 핵심역량

SK biopharmaceuticals

SK바이오팜

국내 제약사 최초로 美 FDA NDA 승인을 독자적으로 획득한 글로벌 종합 제약사

SUNOSI (solriamfetol) tablets

XCOPRI (cenobamate tablets) C

1993 중추신경계 신약 R&D 착수

1996 Solriamfetol FDA IND 획득

2005 Cenobamate FDA IND 획득

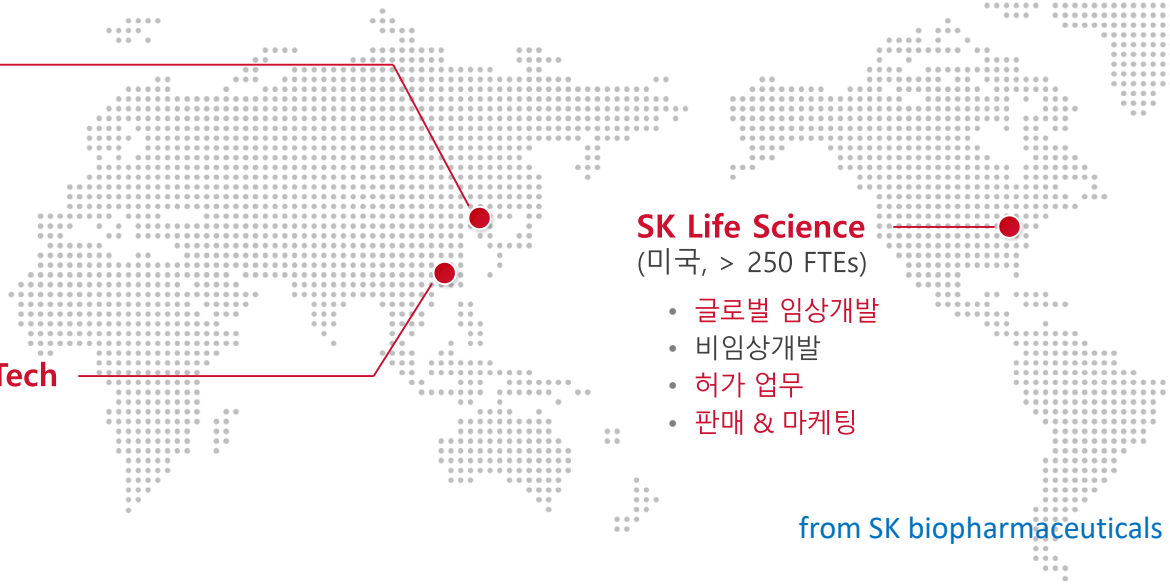
2014 美 Jazz Pharma에 Solriamfetol 기술 수출

2017 Carisbamate FDA 희귀의약품 지정

2018 Cenobamate FDA NDA 신청

2019 Cenomabate FDA NDA 승인, Solriamfetol 출시

2020 Cenobamate 미국 출시, Cenobamate EMA MAA 신청, Solriamfetol EMA MAA 승인



SK Biopharmaceuticals
(한국, > 210 FTEs)

- 후보물질 발굴 및 비임상 개발
- 아시아 임상개발
- 사업개발

SK Bio-Pharm Tech
(중국, 4 FTEs)

SK Life Science
(미국, > 250 FTEs)

- 글로벌 임상개발
- 비임상개발
- 허가 업무
- 판매 & 마케팅

SK biopharmaceuticals

from SK biopharmaceuticals IR Report

SK바이오팜

Hands-on experience from Bench to Market Independently (Full Value Chain Platform)

Project Proposal → Gate 1 → Hit Finding → G2 → Lead ID → G3 → Lead Opt. → G4 → Pre-Clinical → IND → G5 → Phase I → G6 → Phase IIa → G7 → Phase IIb → G8 → Phase III/ NDA → G9 → Sales/ Marketing

Research Center
Translational Research
Process Research

- Concept Build
- Target/Pathway Define
- Assay Tech. Review
- Preliminary Assay Campaign
- Preliminary Hit Analysis
- Project Proposal

- In Vivo VD
- In Vivo Assay Set-up
- Hit Discovery
- TPP Framework

- Preliminary Biology/DMPK Pharmacology
- Preliminary S&T
- → Lead ID
- Ref. Profiling
- TPP Set-up

- Lead Opt.
  - Pharmacol.
  - Chemistry
  - DMPK, S&T
  - Preformu-lation
  - Process R&D
- S4 Candidate Selection
- TPP Update

Transition Groups

- IND-enabled study
  - DMPK
  - Safety & Tox
  - CMC (DS/DP)
- Value-up Study
- IND Filing

Non-Clinical, Clinical, Drug Substance
Drug Product, Regulatory, QA

- Clinical Ph. I (Normal)
  - PK/PD
  - Tolerability
- Chronic Tox.
- CMC(DS/DP)

- Clinical Ph. IIa (Patients, Pilot Study)
  - Efficacy
  - PK/PD
  - Tox./AE
- Chronic Tox.
- CMC(DS/DP)

- Clinical Ph. IIb (Large Patients)
  - Efficacy
  - PK/PD
  - Tox/AE
- Chronic Tox.
- CMC(DS/DP)

- Clinical Ph. III
  - Efficacy
  - PK/PD
  - Tox/AE
- Chronic Tox.
- CMC(DS/DP)

Marketing (Self/Partners)

- US
- EU
- APAC
- ROW

Discovery › CMC › Clinical Development › Regulatory Affairs › Commercialization

SK biopharmaceuticals

II. 뇌전증 (Epilepsy)

- ✓ 뇌전증 개요
- ✓ 뇌전증 시장 및 미충족 수요

SK biopharmaceuticals

뇌전증(Epilepsy)

간질성 발작이 특정한 이유 없이 반복적이고 지속적으로 일어나는 질환

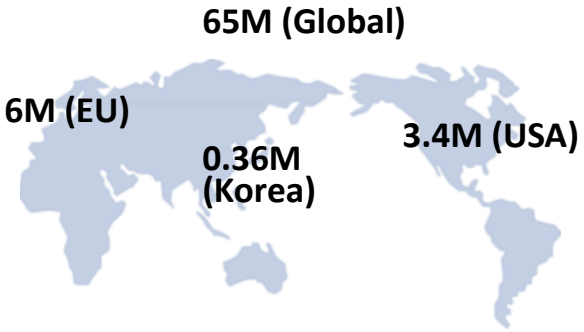
- ✓ Imbalance in excitatory and inhibitory activity in brain
- ✓ Unprovoked and recurrent seizures

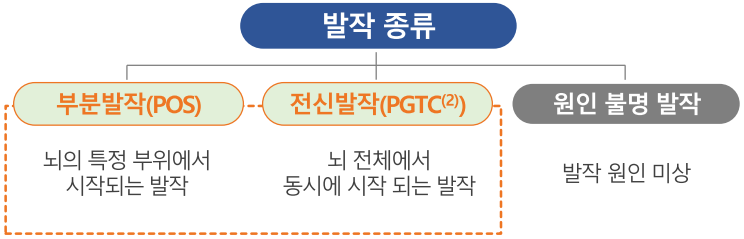
- ✓ Seizure : a sudden rush of electrical activity in the brain
- ✓ Cause of epilepsy : Unknown (60~70%)

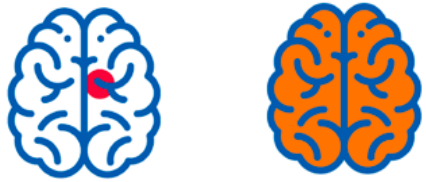
- ✓ 4th most common neurological disorder in US

- ✓ Prevalence rate : ~0.5% (1/200)
- ✓ Most commonly diagnosed age (≤20 or ≥ 65)

- ✓ Treatment
  - ➢ Brain surgery
  - ➢ Ketogenic diet
  - ➢ Vagus nerve stimulator
  - ➢ Anti-epileptic drugs







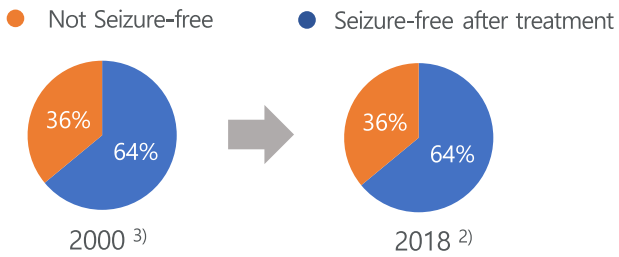
SK biopharmaceuticals

뇌전증(Epilepsy)

뇌전증 시장은 지속적인 성장이 전망되며 새로운 치료 방법에 대한 필요성 및 높은 미충족 수요 존재

- **Expanding Market size** [1)]
  - ✓ Increasing trend from **$8.4 B** (2017) **to $ 9.5 B** (2022) with CAGR 2.7%

- **No Improvement in Seizure-free rate**
  - ✓ Despite 13 new AEDs in the past 20 years, seizure freedom rates have remained nearly the same[2)]
  - ✓ **About 36% of total epilepsy patients are still uncontrolled after using 1-3 AEDs**[2)]



- **Seizure-free rate impacts patients' QoL**
  - ✓ Patients with ≥1 seizure in the past 5 years[4)]
    - 3x more likely to have poor health & overall limitations in life
    - 6x more likely to have depression
  - ✓ Continued seizures increase a patient's risk of SUDEP by 5x times more[5)]

QoL (Quality of Life) ; SUDEP (Sudden, unexpected death in epilepsy)

1) BCC research (2018) ; Decision Resources (2019) ; 2) JAMA Neurol. 1;75(3):279-286 (2018) ; 3) N Engl J Med. 342(5):314-139 (2000) ;
4) *Epilepsia* (2017); The impact of seizures on epilepsy outcomes: A national community-based survey ; 5) *Epilepsia* 52;1150–1159 (2011)

SK biopharmaceuticals

III. Cenobamate

- ✓ Cenobamate 개요
- ✓ 임상 시험 (PoC, Phase II & Phase III)
- ✓ Approval Letter & Label
- ✓ 경쟁력
- ✓ 상업화 조직 및 전략

SK biopharmaceuticals

Cenobamate (미국 제품명 : XCOPRI®)

작용기전(Mechanism of Action)

나트륨 채널 차단
지속 전류 나트륨 채널 차단하여 과도한 신경 흥분 억제

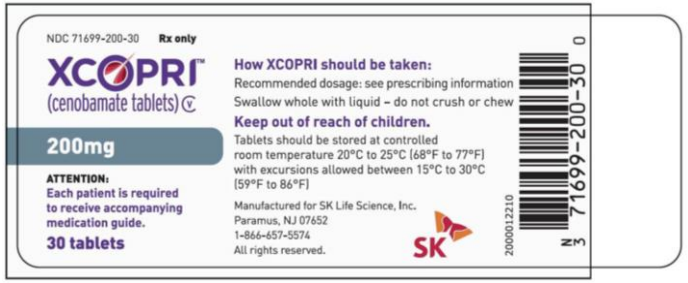
가바(GABA) 수용체 알로스테릭 활성화
억제성 신경전달물질 활성화로 뉴런 자극 약화

이중 작용 기전
광범위 스펙트럼
뇌전증 약효

항목	내용
개발 단계	• FDA 신약 판매 승인 (POS: 단일요법 및 병행요법) • 임상 3상 진행 중 (PGTC)
목표 적응증	• 부분 발작 (POS) • 전신 발작 (PGTC)
상업화	• 미국: 직접 판매 • 유럽: Arvelle 파트너십

주요 Milestones

- November 2019 — FDA 신약 판매 승인
- March 2020 — 마약단속국(DEA) Schedule V 및 EMA 신약허가 심사 개시
- May 2020 — 미국 제품 출시



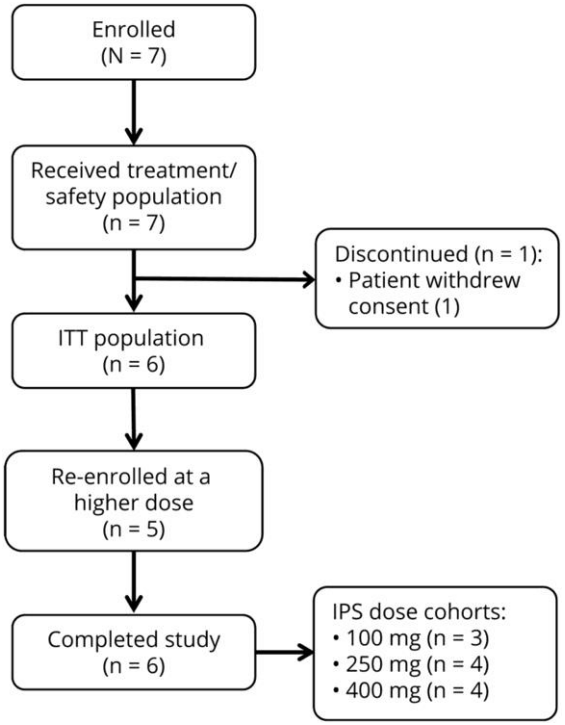
POS: Partial Onset Seizure, PGTC: Primary Generalized Tonic-clonic.

SK biopharmaceuticals

from SK biopharmaceuticals IR Report

Phase IIa : Proof of Concept

Multicenter, single dose, single-blind study (NCT00616148)
Suppression of the photoparoxysmal response in photosensitivity epilepsy



ITT (Intention-to-treat)
IPS (intermittent photic stimulation)

[PK-PD Analysis]

C_{max}, μg/mL	$AUC_{0-t'}$ μg/h/mL	Response	
1.0 – 4.0	*1 – 200*	1/3 (partial)	33%
4.1 – 9.0	*201 – 400*	4/6 (partial)	66%
9.1 – 16.0	***401 - 600***	**2/2 (complete)**	**100%**

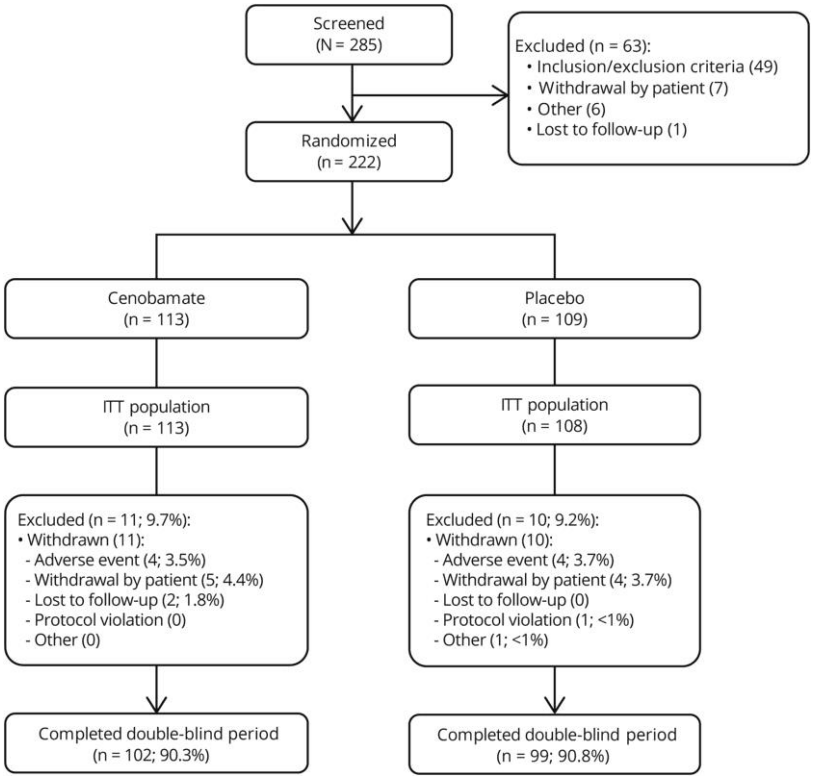
- ✓ **Confirmed the potential of antiepileptic effects**
- ✓ **Target C_{max} > 9μg/mL for robust effect**
- ✓ **Efficacy target dose (for Phase II) : > 100mg, QD**

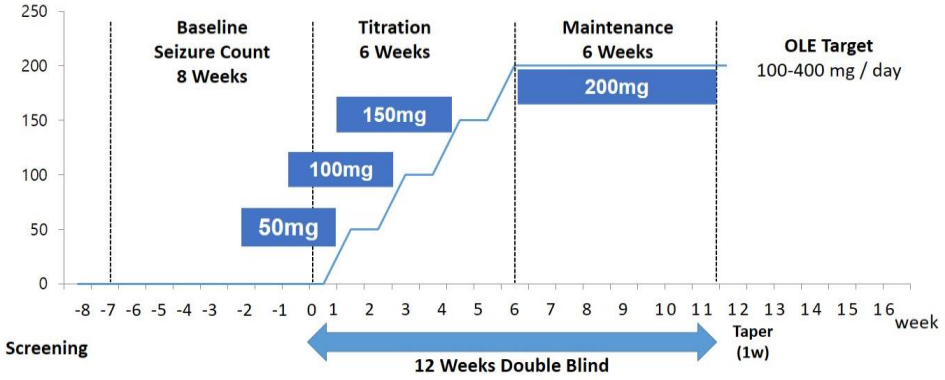
SK biopharmaceuticals

Neurology 2019 ; 93 : e559-e567

Phase II (C013) : Efficacy Study

Multicenter, randomized, double-blind, placebo-controlled study (NCT01397968)





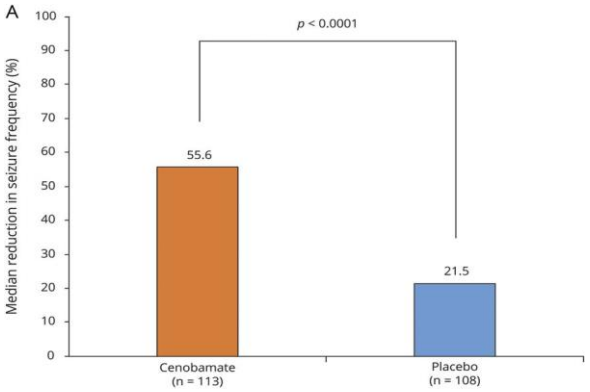
ITT (Intention-to-treat)

Neurology 2020 ; 94 : e2311-e2322

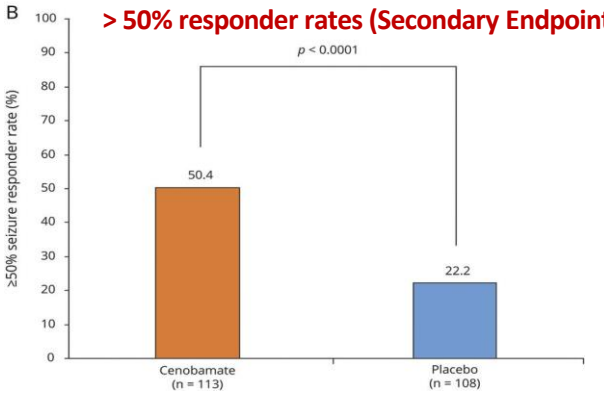
Phase II (C013) : Efficacy Study

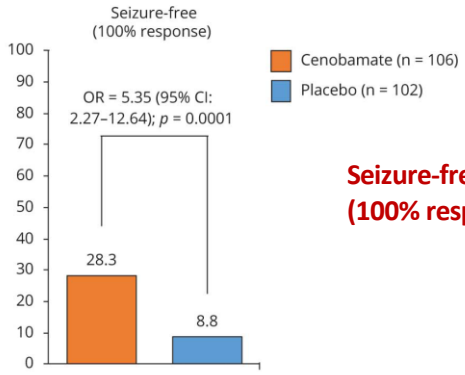
Multicenter, randomized, double-blind, placebo-controlled study (NCT01397968)

Median percent reduction in seizure frequency (Primary Endpoint)



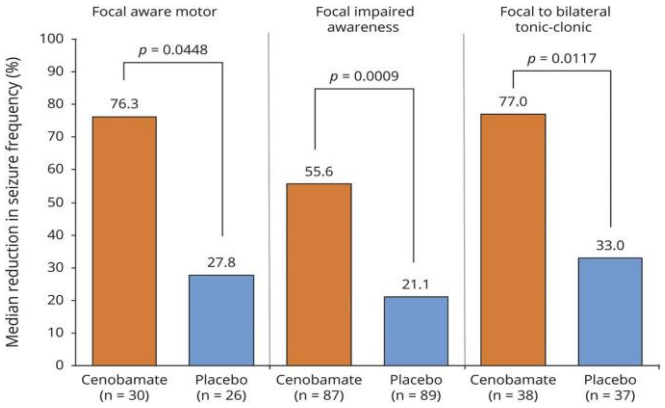
> 50% responder rates (Secondary Endpoint)





Seizure-free (100% response)

Median percent reduction for focal seizure types



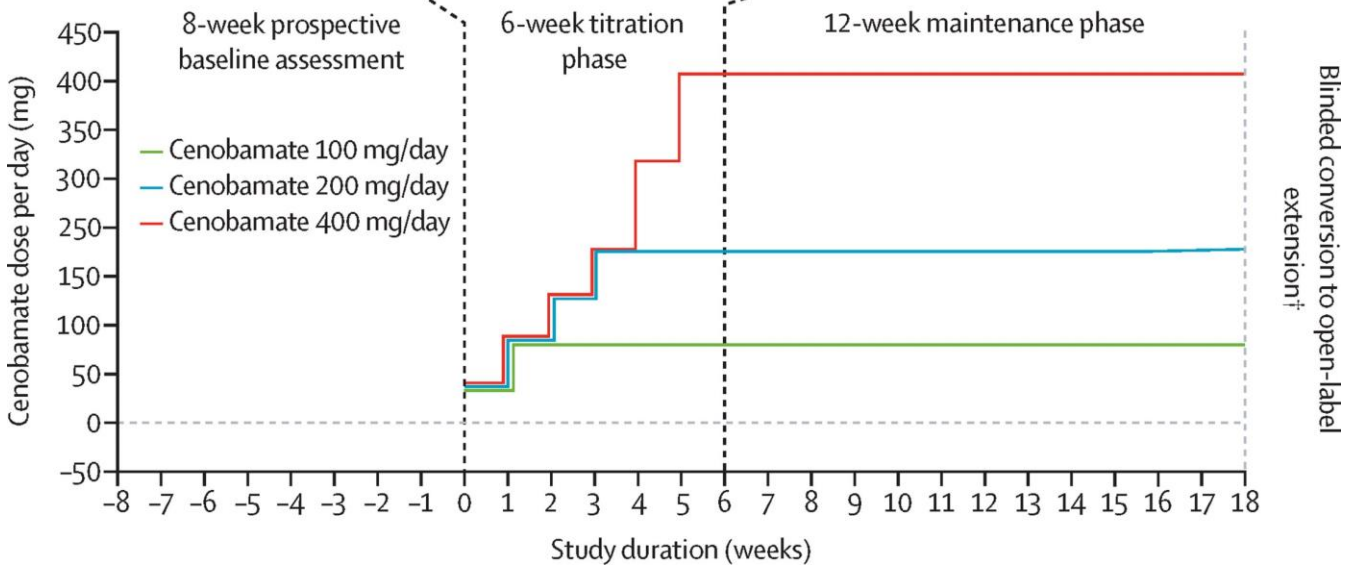
Neurology 2020 ; 94 : e2311-e2322

SK biopharmaceuticals

Phase II (C017) : Efficacy Study

Multicenter, randomized, double-blind, placebo-controlled study (NCT01866111)

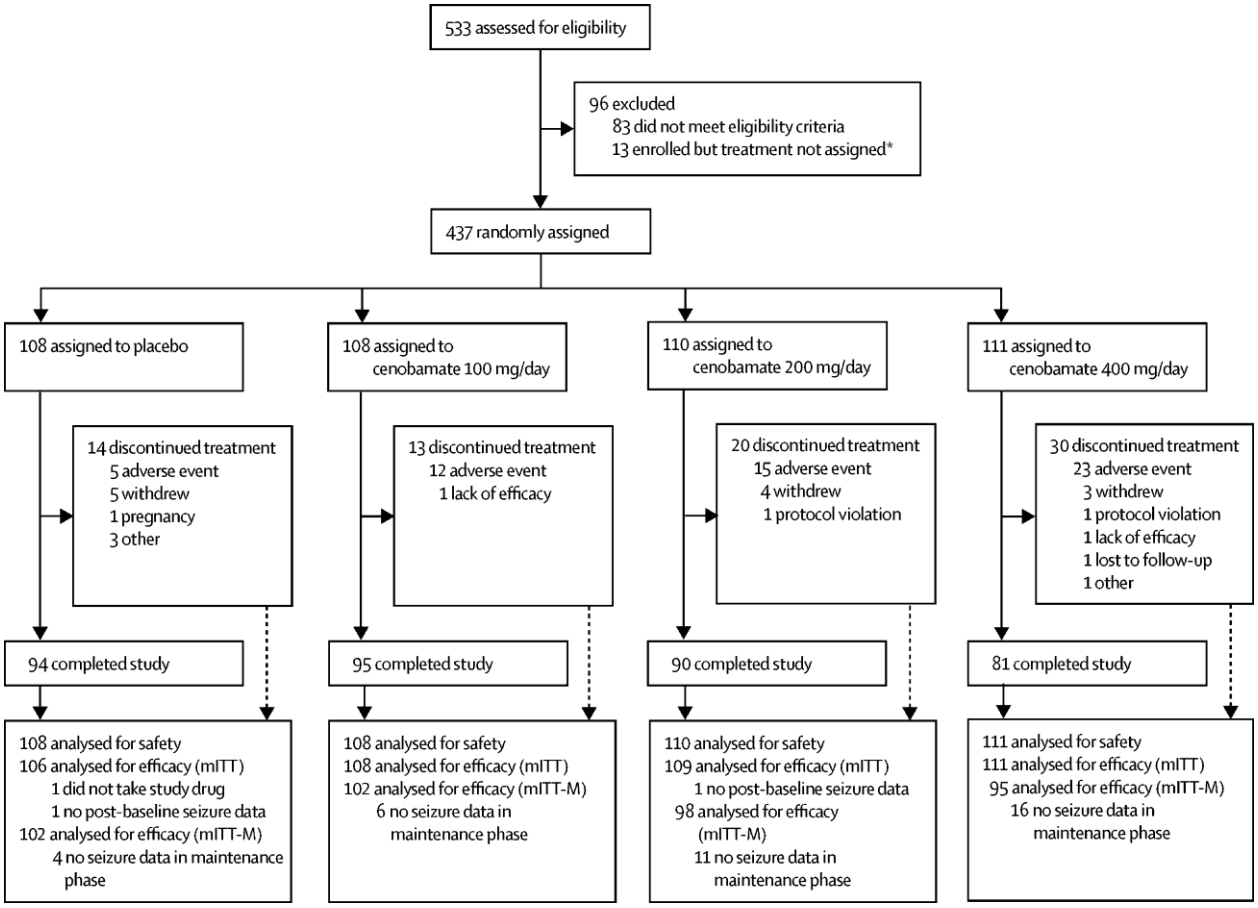
Week 1*	Week 2	Week 3	Week 4	Week 5	Week 6
50 mg/day	100 mg/day	150 mg/day	200 mg/day	300 mg/day	400 mg/day



Lancet Neurol 2020 ; 19 : 38-48

Phase II (C017) : Efficacy Study

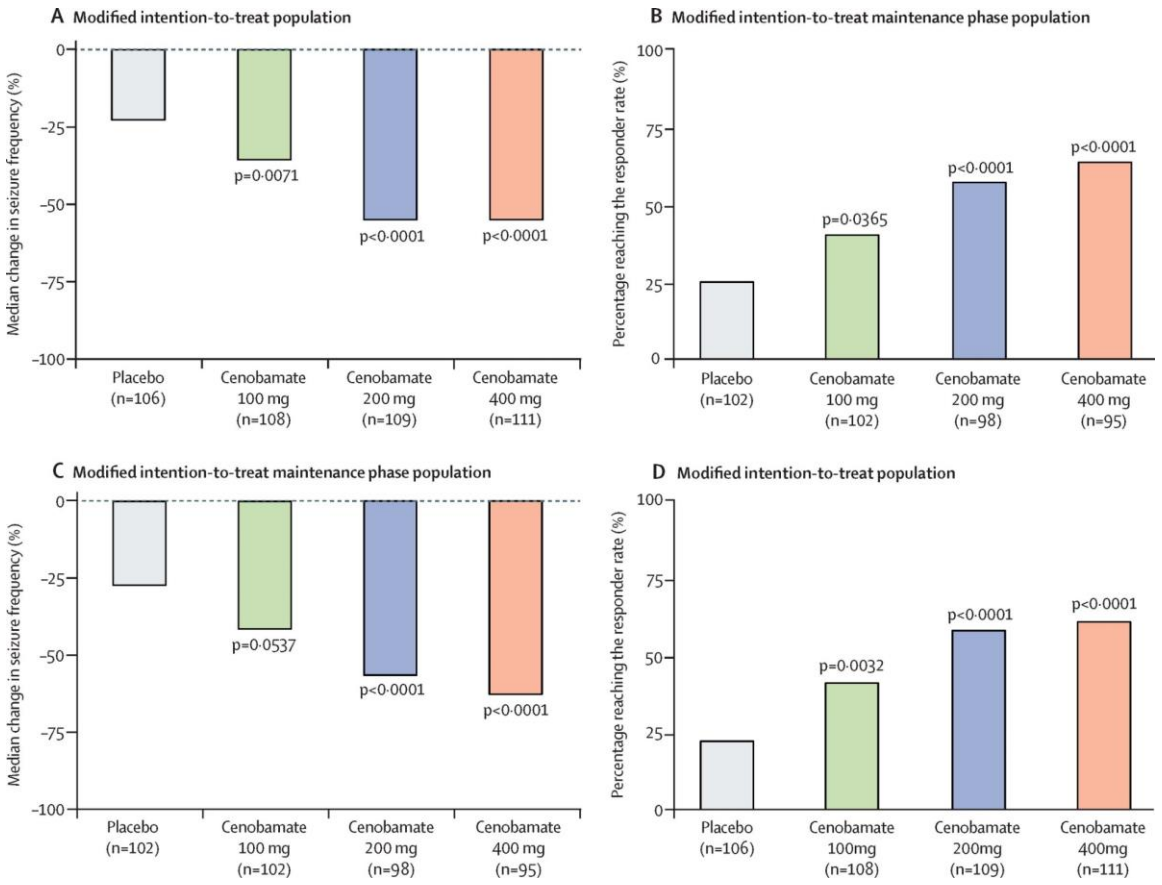
Multicenter, randomized, double-blind, placebo-controlled study (NCT01866111)



Lancet Neurol 2020 ; 19 : 38-48

Phase II (C017) : Efficacy Study

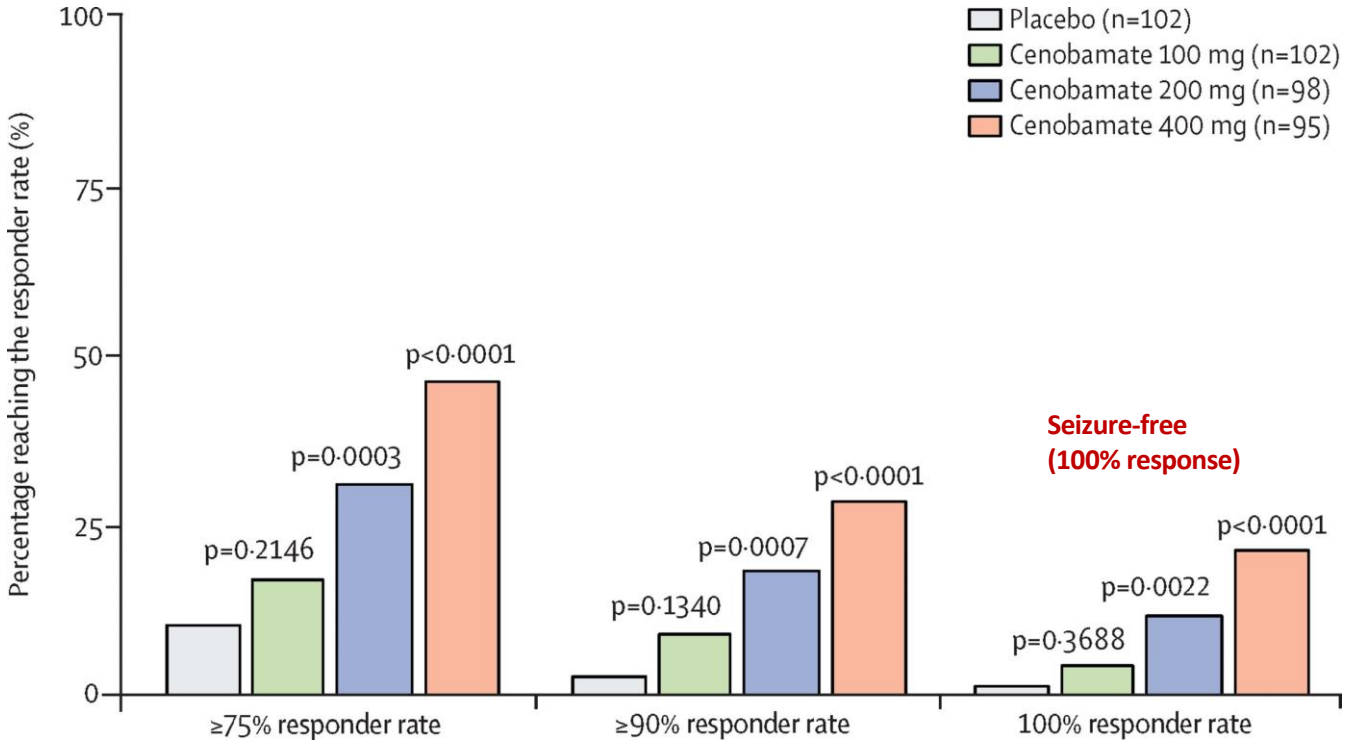
Multicenter, randomized, double-blind, placebo-controlled study (NCT01866111)



Lancet Neurol 2020 ; 19 : 38-48

Phase II (C017) : Efficacy Study

Multicenter, randomized, double-blind, placebo-controlled study (NCT01866111)

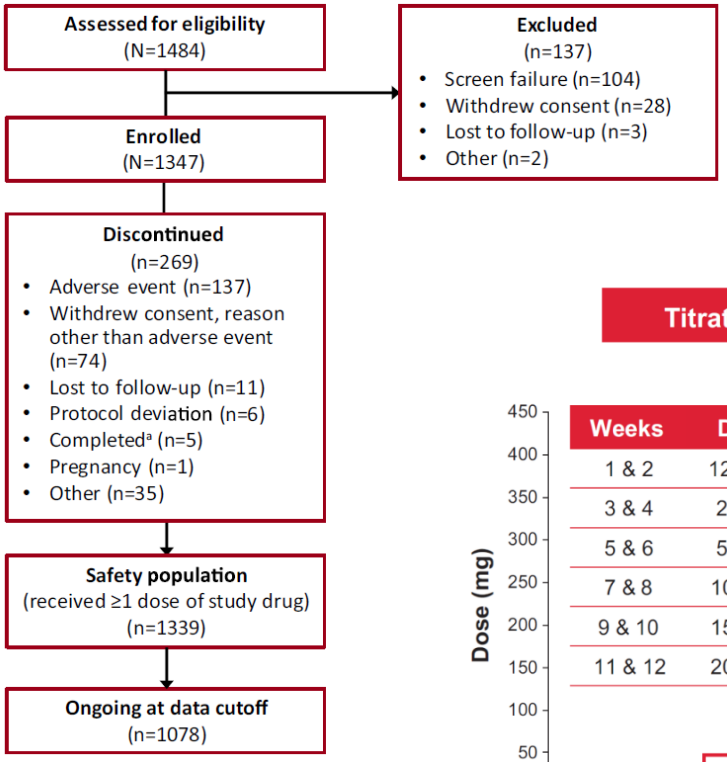


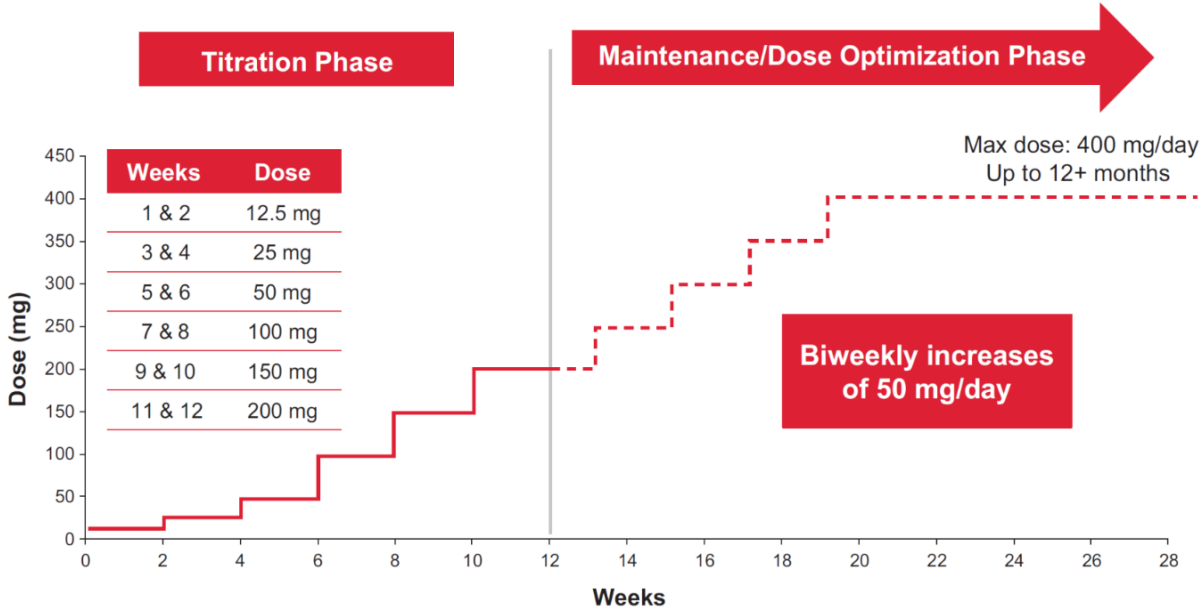
SK biopharmaceuticals

Lancet Neurol 2020 ; 19 : 38-48

Phase III (C021) : Safety Study

Multicenter, open-label study (NCT02535091)





Epilepsia 2020 ; 61 : 1099-1108

Phase III (C021) : Safety Study

Multicenter, open-label study (NCT02535091)

- ✓ **High retention (82.9%_1110/1339, over 6 months)**
  → **Good tolerability**
- ✓ **Most AEs : CNS related**
- ✓ **No cases of DRESS**
  → **low start dose & slow titration rate may lower the risk of DRESS**

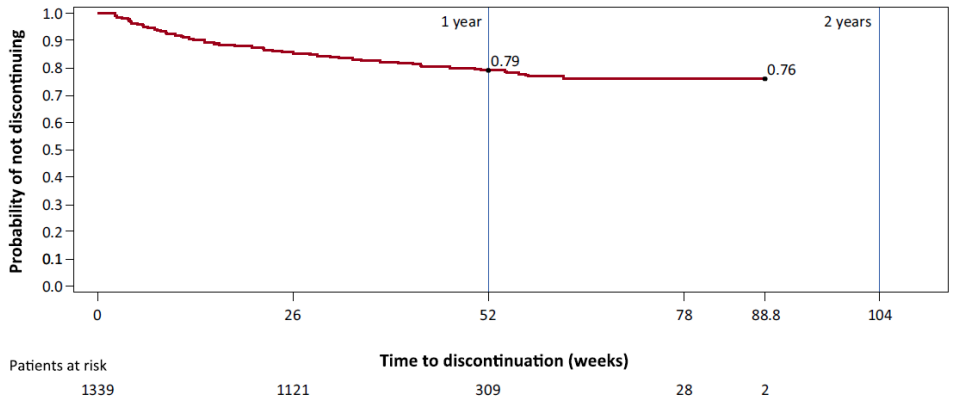


TABLE 2 Summary of treatment-emergent adverse events (safety population)

	Cenobamate patients, n = 1339
Any TEAE	1128 (84.2)
TEAEs leading to discontinuation	147 (11.0)
Treatment-related TEAEs	935 (69.8)
Serious TEAEs	108 (8.1)
TEAEs ≥5%	
Somnolence	376 (28.1)
Dizziness	316 (23.6)
Fatigue	222 (16.6)
Headache	152 (11.4)
Viral upper respiratory tract infection	98 (7.3)
Upper respiratory tract infection	82 (6.1)
Nausea	80 (6.0)
Diplopia	78 (5.8)
Balance disorder	74 (5.5)

DRESS (Drug reaction with eosinophilia and systemic symptoms)
TEAE (Treatment-emergent adverse event)

Epilepsia 2020 ; 61 : 1099-1108

SK biopharmaceuticals

Approval Letter (*November, 21th, 2019*)

U.S. FOOD & DRUG ADMINISTRATION

NDA 212839

NDA APPROVAL

SK Life Science, Inc.
Attention: Darshan Patel
Head, Global Regulatory Affairs
461 From Road, 5th Floor
Paramus, NJ 07652

Dear Mr. Patel:

Please refer to your new drug application (NDA) dated and received November 21, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xcopri (cenobamate) 12.5, 25, 50, 100, 150, and 200 mg tablets.

This NDA provides for the use of Xcopri (cenobamate) tablets for the treatment of partial-onset seizures in adult patients.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved for use as recommended in the enclosed agreed-upon labeling.

SK biopharmaceuticals

www.fda.gov
Drug Approval Package: XCOPRI

Label : Cenobamate (미국 제품명 : XCOPRI®)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XCOPRI safely and effectively. See full prescribing information for XCOPRI.

XCOPRI® (cenobamate tablets), for oral use, [controlled substance schedule pending]
Initial U.S. Approval: XXXX [pending controlled substance scheduling]

INDICATIONS AND USAGE

XCOPRI is indicated for the treatment of partial-onset seizures in adult patients. (1)

DOSAGE AND ADMINISTRATION

- Swallow tablets whole. Do not crush or chew. (2.1)
- The recommended initial dosage of XCOPRI is 12.5 mg once daily, titrated to the recommended maintenance dosage of 200 mg once daily. The recommended titration schedule should not be exceeded. The maximum dosage is 400 mg once daily. (2.2)
- Hepatic impairment: For patients with mild or moderate hepatic impairment, the maximum recommended dosage is 200 mg once daily. (2.3, 8.7, 12.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. (3)

CONTRAINDICATIONS

- Hypersensitivity to cenobamate or any of the inactive ingredients in XCOPRI. (4)
- Familial Short QT syndrome. (4)

WARNINGS AND PRECAUTIONS

- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity* Discontinue if no alternate etiology. (5.1)
- *QT Shortening* Use caution when administering XCOPRI with other drugs that shorten the QT interval (5.2)
- *Suicidal Behavior and Ideation*: Monitor patients for suicidal behavior and ideation. (5.3)
- *Neurological Adverse Reactions*: Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on XCOPRI. Concomitant use with other CNS depressants or alcohol may have additive effects. (5.4)
- *Withdrawal of Antiepileptic Drugs*: XCOPRI should be gradually withdrawn to minimize the potential of increased seizure frequency. (5.5)

ADVERSE REACTIONS

The most common adverse reactions in patients receiving XCOPRI (at least 10% for XCOPRI and more frequently than placebo) include somnolence, dizziness, fatigue, diplopia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SK Life Science, Inc. at 1-866-657-5574 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Phenytoin: Gradually decrease phenytoin dosage by up to 50% (7.1)
- Phenobarbital and Clobazam: Reduce dosage as needed when used concomitantly with XCOPRI. (7.1)
- Lamotrigine, Carbamazepine: Increase dosage as needed when used concomitantly with XCOPRI. (7.1)
- CYP2B6 and CYP3A Substrates: Increase dosage as needed when used concomitantly with XCOPRI. (7.1)
- CYP2C19 Substrates: Reduce dosage as needed when used concomitantly with XCOPRI. (7.1)
- Oral Contraceptives: Effectiveness of hormonal oral contraceptives may be reduced when administered concomitantly with XCOPRI. Women should use additional or alternative non-hormonal birth control. (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Renal Impairment: Use with caution and dosage reduction may be considered in patients with mild to moderate (CLcr 30 to < 90 mL/min) and severe (CLcr < 30 mL/min) renal impairment. Use not recommended in end-stage renal disease (CLcr < 15 mL/min) undergoing dialysis. (8.6)
- Hepatic Impairment: Use with caution in patients with mild to moderate hepatic impairment; lower maximum dosage and additional dosage reduction may be considered. Use of XCOPRI in patients with severe hepatic impairment is not recommended. (2.3, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2019

www.fda.gov
Drug Approval Package: XCOPRI

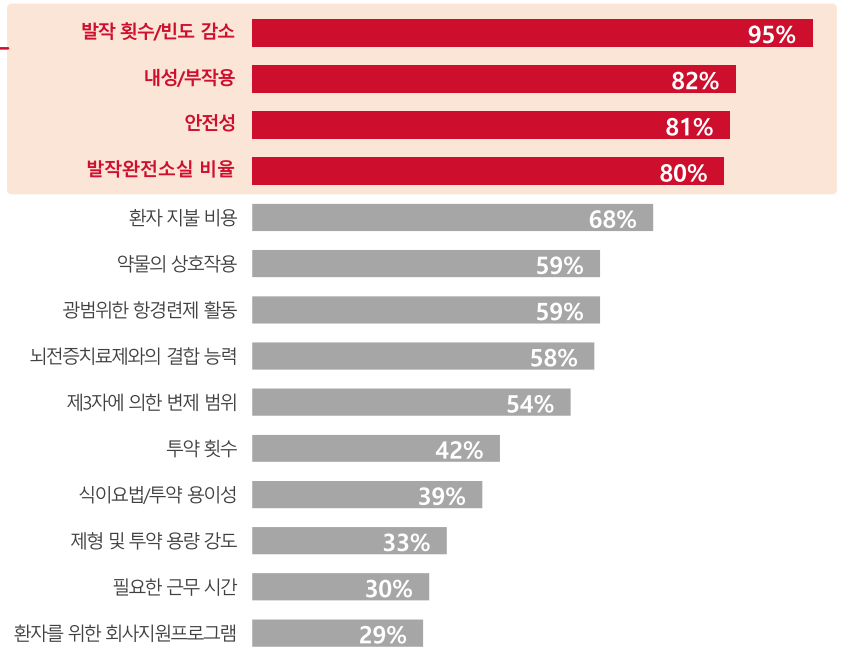
SK biopharmaceuticals

Cenobamate 경쟁력

기존 뇌전증 치료제의 미충족 의료 수요 충족으로 인한 높은 경쟁력 확보

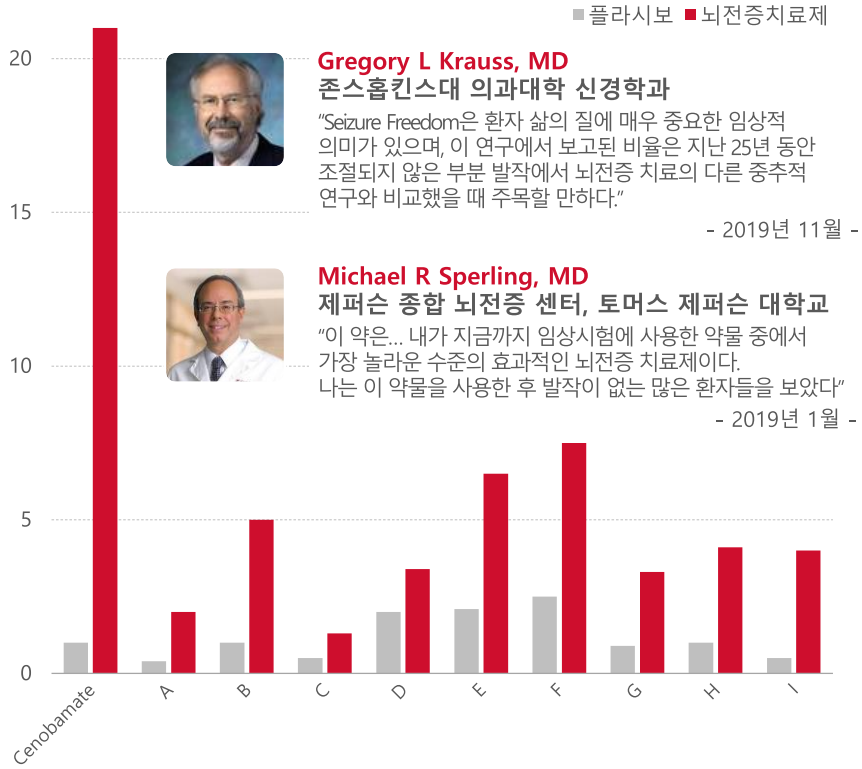
미국 의료 전문가의 뇌전증 치료제 선택시 주요 고려사항

미국 의료 전문가(1)의 뇌전증 치료제 처방시 주요 고려사항 4가지 (중요도 순서) : 발작 감소율 / 내성 / 안전성 / 발작완전소실 비율



참조 : 2019 ATU Study, Dominion Group
비고 : (1) 의료전문가(HCPs, Healthcare Professionals)

뇌전증 치료제 연구에서 발작완전소실 비율



Gregory L Krauss, MD
존스홉킨스대 의과대학 신경학과
"Seizure Freedom은 환자 삶의 질에 매우 중요한 임상적 의미가 있으며, 이 연구에서 보고된 비율은 지난 25년 동안 조절되지 않은 부분 발작에서 뇌전증 치료의 다른 중추적 연구와 비교했을 때 주목할 만하다."
- 2019년 11월 -

Michael R Sperling, MD
제퍼슨 종합 뇌전증 센터, 토머스 제퍼슨 대학교
"이 약은... 내가 지금까지 임상시험에 사용한 약물 중에서 가장 놀라운 수준의 효과적인 뇌전증 치료제이다. 나는 이 약물을 사용한 후 발작이 없는 많은 환자들을 보았다"
- 2019년 1월 -

임상결과 비교 데이터는 직접비교(Head to Head)임상에 따른 연구 결과값이 아님

from SK biopharmaceuticals IR Report

SK biopharmaceuticals

미국 상업화 조직 및 전략

성공적 출시를 위한 영업전략 수립 및 미국 내 상업화 조직 구축 완료, 판매 진행 중

20년 이상 경력자들로 구성된 리더십 팀

Sebby Borriello
CCO

Johnson & Johnson
ORTHO-McNEIL

Jeff Crowther
VP of S&M

Johnson & Johnson
Adheris

Robert Polans
VP of Market Access

Johnson & Johnson
VALEANT

Matthew Linkewich
VP of C-Operations

Johnson & Johnson
IMS ORTHO-McNEIL
imshealth AstraZeneca

성공적 제품 출시를 위한 체계적 영업조직 구축

효과적인 영업 및 마케팅을 위해 최고의 전문 영업사원 대상 체계화된 Training Program

- 글로벌 제약회사에서 **20년 이상 경력**을 가진 **18명의 전문가들**로 구성된 최고의 영업 조직
- 미국 內 영업지역 확대를 위한 **100명 이상의 전문 영업조직 구축**

영업 조직 배치 및 핵심 영업 대상

234개의 뇌전증 센터와 핵심 타겟인 의료전문가 12,791명 대상

핵심 타겟 그룹

1	2	3
234	12,791	23,640
뇌전증 센터 (1,617 전문의(HCPs)	Primary Segment 1 – 3	Segment 4

뇌전증 센터의 영업 극대화를 위한 조직적인 영업

완벽한 지역별 커버를 위한 영업 조직 설계 최적화

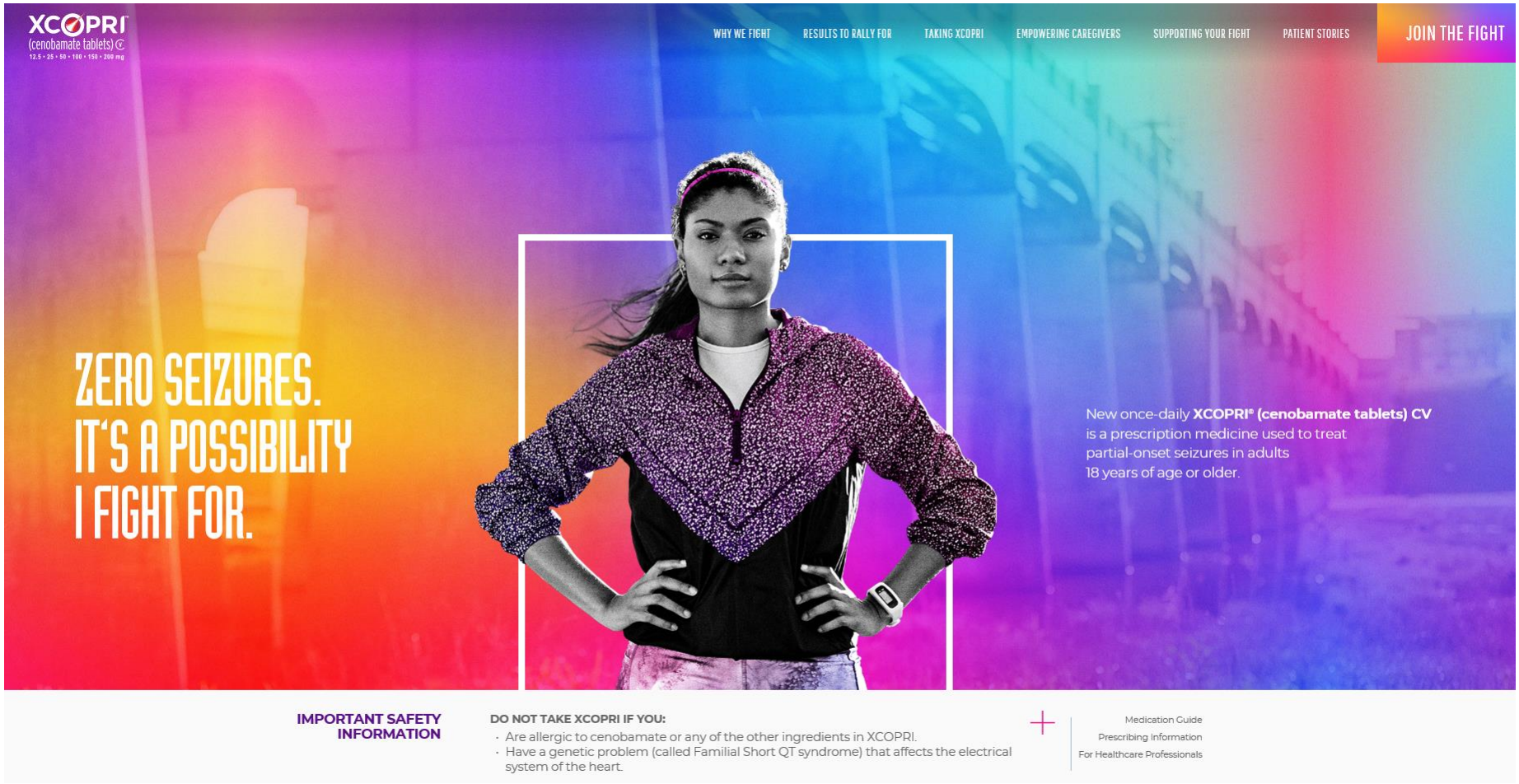
Target Group의 효과적 관리 및 처방건수 증가를 위해 +100개 지역 중심으로 영업 조직 최적 운영

93%	99%+	99%+
뇌전증 센터	Target 전문의	Target 브랜드 처방

from SK biopharmaceuticals IR Report

SK biopharmaceuticals

미국 제품 사이트 (https://www.xcopri.com)



SK biopharmaceuticals

Thanks