임상 진입 시 고려해야할 목표 제품 특성(TPP)

양 혜 경


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BioScience
01. 신약 개발 과정
02. 신약 허가 사례
03. 목표 제품 특성


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01
신약 개발 과정

의약품 개발부터 사용까지 전주기 체계도

GLP: Good Laboratory Practice
GCP: Good Clinical Practice
GMP: Good Manufacturing Practice
Investigational New Drug(IND) Application - 임상시험 계획 승인 신청
New Drug Application(NDA) - 품목 허가 신청

의약품 품목 허가심사 절차의 이해 2017.07

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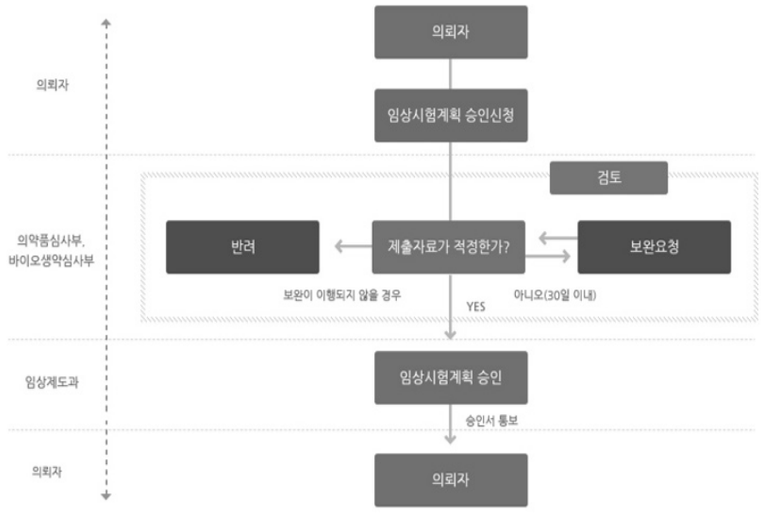
임상시험계획 승인절차



의약품안전나라 > 의약품등 정보 > 임상시험정보 > 임상시험이란 > 임상시험 승인절차 (mfds.go.kr)

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임상시험 관련 규정 및 공무원 지침서

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관련 규정: '국가법령정보센터'에서 검색 가능, 링크: 국가법령정보센터 (law.go.kr)

1) 「약사법」제34조 링크: 약사법 (law.go.kr)

2) 「의약품 등의 안전에 관한 규칙」 [시행 2022. 3. 9.] [총리령 제1683호, 2021. 3. 8., 일부개정]

링크: 의약품 등의 안전에 관한 규칙 | 국가법령정보센터 | 현행법령 > 법령명 (law.go.kr)

3) 「의약품 임상시험 계획 승인에 관한 규정」 [시행 2018. 10. 25.] [식품의약품안전처고시 제2018-77호, 2018. 10. 25., 일부개정]

링크: 의약품 임상시험 계획 승인에 관한 규정 | 국가법령정보센터 | 현행행정규칙 > 규칙명 (law.go.kr)

4) 「의약품의 품목허가·신고·심사 규정 」 [시행 2021. 11. 11.] [식품의약품안전처고시 제2021-90호, 2021. 11. 11., 일부개정]

링크: 의약품의 품목허가·신고·심사 규정 (law.go.kr)

공무원 지침서

GRP-MaPP-심사기준-01(지침서-0113-04)[2022.2.10 개정] 의약품 임상시험계획(변경)승인 검토서 작성 기준

GRP-MaPP-허가업무_01 (지침서-0940-04)[2022.4.6 개정] 의약품 허가사항 검토시 일반적 고려사항

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정의: 약사법 제2조 제 15호

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의약품이란 다음 각 목의 어느 하나에 해당하는 물품을 말한다.

가. 대한민국약전(大韓民國藥典)에 실린 물품 중 의약외품이 아닌 것

나. 사람이나 동물의 질병을 진단・치료・경감・처치 또는 예방할 목적으로 사용하는 물품 중 기구・기계 또는 장치가 아닌 것

다. 사람이나 동물의 구조와 기능에 약리학적(藥理學的) 영향을 줄 목적으로 사용하는 물품 중 기구・기계 또는 장치가 아닌 것

임상시험이란 의약품 등의 안전성과 유효성을 증명하기 위하여 사람을 대상으로 해당 약물의 약동(藥動) 약력(藥力) 약리 임상적 효과를 확인하고 이상반응을 조사하는 시험(생물학적 동등성시험을 포함한다)

- 다만, 「첨단재생의료 및 첨단바이오의약품 안전 및 지원에 관한 법률」 제2조제3호에 따른 첨단재생의료 임상연구는 제외

비임상 시험이란 사람의 건강에 영향을 미치는 시험물질의 성질이나 안전성에 관한 각종 자료를 얻기 위하여 실험실과 같은 조건에서 동물・식물・미생물과 물리적・화학적 매체 또는 이들의 구성 성분으로 이루어진 것을 사용하여 실시하는 시험을 말한다.

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- **Investigational New Drug(IND) Application** – 임상시험 계획 승인 신청
- **New Drug Application(NDA)** - 품목 허가 신청
- **상업 임상시험(Sponsor-initiated trial, SIT)**

  -개발 중인 신약

  -신조성, 신투여경로, 신제형의 약품

  -효능효과, 용법용량 등의 변경

  -연구용 임상

  -주요 허가사항의 변경

- **연구자 임상시험(Investigator-initiated trial, IIT)**
  - 임상시험자가 외부의 의뢰없이 안전성유효성이 검증되지 않은 의약품 또는 시판중인 의약품으로 허가(신고)되지 아니한 새로운 효능효과, 용법용량에 대해 독자적으로 수행하는 임상시험

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임상시험의 단계

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- **제1상 임상시험(임상약리시험 등)**
  - 내약성 평가, 약동학과 약력학 정의/서술, 약물대사와 상호작용 조사, 치료효과 추정을 목적으로하는 임상 약리시험 등
  - 용량-내약성 임상시험, 단독과 반복 투여에 따른 약동학/약력학 임상시험, 약물 상호작용 임상시험
- **제2상 임상시험(치료적 탐색 임상시험)**
  - 목표 적응증에 대한 탐구, 후속 시험을 위한 용량 추정, 치료확증 시험을 위한 시험설계, 평가 항목, 평가 방법에 대한 근거 제공을 목적으로 하는 치료적 탐색 임상시험 등
  - 대리 약리학적 평가 또는 임상적 평가 방법을 사용하여 잘 정의된 소수의 환자에서의 비교적 단기간에 걸친 초기 임상시험, 용량-반응 탐색 임상시험 등
- **제3상 임상시험(치료적 확증 임상시험)**
  - 유효성 입증/확증, 안전성 자료 확립, 임상적용을 위한 이익과 위험의 상대 평가 근거 제공, 용량과 반응에 대한 관계 확립을 목적으로 하는 치료적 확증 임상시험 등
  - 유효성 확립을 위한 적절하고 잘 통제된 임상시험, 무작위 배정에 의한 용량-반응 임상시험, 안전성 임상시험, 이환율/사망률을 위한 임상시험, 비교적 간단한 대규모 임상시험, 대조군을 이용한 비교 임상시험 등

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임상시험계획 승인 신청 시 제출 자료 : 의약품 등의 안전에 관한 규칙 제 24조제1항에 따른 제출 자료 항목

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1. **임상시험 계획서** 또는 임상시험 변경계획서
2. **개발계획**
3. 별표 1의 의약품 제조 및 품질관리기준 및 별표 4의2의 임상시험용의약품 제조 및 품질관리기준에 맞게 제조되었음을 증명하는 서류 또는 자료
4. 임상시험용의약품 관련 **제조 및 품질에 관한 자료**
5. **비임상시험성적**에 관한 자료
6. 시험약의 **과거 임상적 사용경험**에 관한 자료(제출할 수 있는 경우만 해당)
7. 임상시험 관련 실시기관, 시험자 및 수탁기관 등에 관한 자료
8. **임상시험 피해자 보상에 관한 규약**
9. **시험대상자 동의서 서식**
10. **임상시험자자료집**

의약품안전나라 > 의약품등 정보 > 임상시험정보 > 임상시험이란 > 임상시험 승인절차 (mfds.go.kr)

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임상시험계획서에 수록되어야 할 내용 : 의약품 등의 안전에 관한 규칙 제 24조제2항

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1. 시험의 제목, 단계, 계획서 식별번호 및 제개정이력 등
2. 시험계획서 요약
3. 서론(배경, 이론적 근거, 유익성·위험성 평가 및 용량 설정 근거 등)
4. 시험의 목적
5. 시험모집단(대상자수, 선정기준, 제외기준 및 중도탈락기준 등)
6. 시험 설계 내용(시험기간, 시험군·대조군, 배정, 눈가림 및 흐름도 등)
7. 시험 종료 및 조기중단 기준
8. 임상시험용의약품의 정보 및 관리(표시 및 포장, 투여경로, 투여방법, 보관조건, 수불관리, 회수 및 폐기 등)

의약품안전나라 > 의약품등 정보 > 임상시험정보 > 임상시험이란 > 임상시험 승인절차 (mfds.go.kr)

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임상시험계획서에 수록되어야 할 내용 : 의약품 등의 안전에 관한 규칙 제 24조제2항

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9. 시험의 방법 및 투약계획 등(투여 및 치료일정, 병용약물, 투여금지 약물 및 치료순응도 등)
10. 시험 절차 및 평가(방문일정, 시험일정표, 유효성·안전성 평가변수와 평가 및 이상반응 보고 등)
11. 자료 분석 및 통계학적 고려사항(분석군, 통계분석방법, 판정기준, 분석시기 및 대상자수 설정근거 등)
12. 자료 관리(기록, 수집, 접근, 보호 및 보관 등)
13. 윤리적 고려사항 및 행정적 절차(임상시험관리기준 및 동의절차 등 규정, 윤리준수, 대상자 안전보호 대책, 결과발표, 환자기록 비밀유지, 품질관리 및 신뢰성 보증 등)
14. 임상시험을 하려는 자(이하 "임상시험 의뢰자"라 한다)의 정보, 시험책임자 성명 및 직책
15. 그 밖에 임상시험을 안전하게 과학적으로 실시하기 위하여 필요한 사항

의약품안전나라 > 의약품등 정보 > 임상시험정보 > 임상시험이란 > 임상시험 승인절차 (mfds.go.kr)

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02
신약 허가 사례

신약 허가 사례 – Tirzepatide

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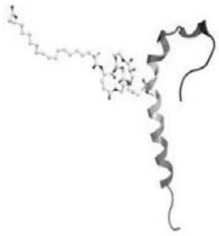
- Tirzepatide(상품명: Mounjaro)
- FDA approval date: 2022.05.13, 국내: 미승인
- 제2형 당뇨병 피하주사 약제: GIP & GLP-1 receptor 에 대한 dual agonist



- 참고) 국내 허가된 GLP-1 receptor agonist

당뇨약: 오젬픽(semaglutide), 트루리시티(dulaglutide), 빅토자(liraglutide) 등

비만약: 삭센다(liraglutide)

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Tirzepatide FDA Label

Approval Date: 2022.05.13

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

MOUNJARO™ (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

---------- INDICATIONS AND USAGE ----------

MOUNJARO™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis (1, 5.2)
- Is not indicated for use in patients with type 1 diabetes mellitus (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1)
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15 mg subcutaneously once weekly (2.1).
- Administer once weekly at any time of day, with or without meals. (2.2)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- Rotate injection sites with each dose.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)

---------- CONTRAINDICATIONS ----------

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1)
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (4, 5.4)

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Tirzepatide FDA Label

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---------- WARNINGS AND PRECAUTIONS ----------

- *Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.2)
- *Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:* Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. (5.3)
- *Hypersensitivity Reactions:* Hypersensitivity reactions have been reported. Discontinue MOUNJARO if suspected. (5.4)
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *Severe Gastrointestinal Disease:* Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.6)
- *Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy:* Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.7)
- *Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated. (5.8)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions, reported in ≥5% of patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

MOUNJARO delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy:* Based on animal study, may cause fetal harm. (8.1)
- *Females of Reproductive Potential:* Advise females using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (7.2, 8.3, 12.3)

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Tirzepatide : Overall Timeline of Clinical Program

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Study	Description	Subject No.	2016 2Q	3Q	4Q	2017 1Q	2Q	3Q	4Q	2018 1Q	2Q	3Q	4Q	2019 1Q	2Q	3Q	4Q	2020 1Q	2Q	3Q	4Q	2021 1Q	2Q	3Q	4Q	2022 1Q	2Q	3Q	4Q
Biopharmaceutic studies																													
GPGE	Formulation	46																											
GPHI	Effect of BMI	54																											
GPGS	Effect of injection device	45																											
Clinical Pharmacology studies																													
GPGA	SAD, 4-week MAD, safety, PK, PD	198																											
GPGC	MAD, PK, PD (Japaneses T2DM)	66																											
GPGG	Effect of renal impairment	45																											
GPGQ	Effect of hepatic impairment	32																											
GPGR	Effect on combined OC*	40																											
GPGT	Effect on pancreatic cell function	117																											
GPHX	Disposition of radioactivity and PK	6																											
Phase 2																													
GPGB	26- week diet/exercise control ± Met	318																											
GPGF	12- week diet/exercise control ± Met	111																											
Phase 3																													
GPGH	Met ± SGLT-2i	1444																											
GPGI	Insulin glargine ± Met	475																											
GPGK	diet/exercise	478																											
GPGL	diet/exercise control ± Met	1879																											
GPGM	T2DM with increased CV risk	2022																											
GPGO	Japanese (mono)	636																											
GPGP	Japanese (1 OAM)	443																											

*OC = oral contraceptive; OAM = oral antihyperglycemic medication
19 completed clinical studies, data cutoff date June 2, 2021, Total Subject No. 8455

FDA Approval
2022.05.13

AIMS BioScience

Tirzepatide : Phase 1 Study

18

Title: A Single- and Multiple-Ascending Dose Study in Healthy Subjects to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176 and Multiple Doses in Patients With Type 2 Diabetes Mellitus (NCT02759107)

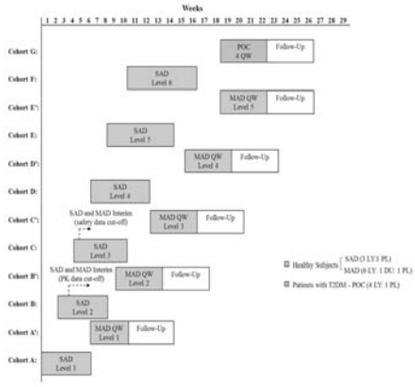
Subject No. : 198 participants (2 sites, 2 countries: United States, Singapore)

Design : Multicenter, randomised, placebo-controlled, double-blind study comprised of three parts: single-ascending dose (SAD), and 4-week multiple-ascending dose (MAD) in healthy subjects, followed by a 4-week multiple-dose Phase 1b proof-of-concept (POC) in T2DM

Primary Outcome : Number of Participants with One or More Serious Adverse Event(s) (SAEs) Considered by the Investigator to be Related to Study Drug Administration [Time Frame: Baseline through Day 43 (Part A) or Day 57 (Part B and C)]

Secondary Outcome : PK (AUC of LY3298176), PD (AUC of Glucose)

- Single-Ascending Dose(SAD) study
- Multiple-Ascending Dose(MAD) study
- Proof-of-Concept(PoC) study



The MAD part, POC parts, and follow-up period lasted for 4 weeks. Note: This is a general schematic of the study design, dose levels may be repeated or cohorts added. QW=once weekly dosing[11]

Molecular metabolism, 2018, 18: 3-14.

Tirzepatide : Phase 2 Study - 1

19

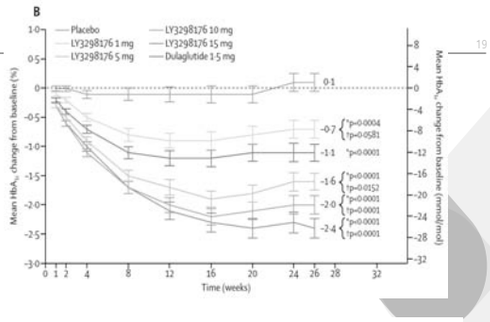
Title: A Phase 2 Study of Once-Weekly LY3298176 Compared With Placebo and Dulaglutide in Patients With Type 2 Diabetes Mellitus (NCT03131687)

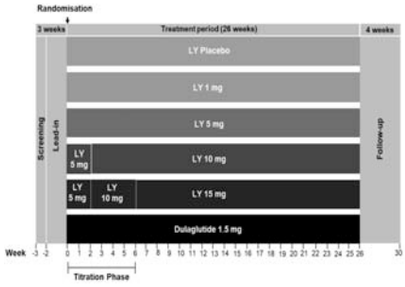
Subject No. : 318 participants (47 sites, 4 countries: Poland, Puerto Rico, Slovakia, United States)

Design : Multicenter, Double-blind (Participant, Investigator), Parallel-group, placebo- and active comparator- controlled, randomized phase 2 trial

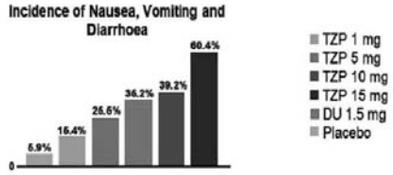
Primary Outcome : Change from baseline to Week 26 in HbA1c

Secondary Outcome : Change From Baseline in Body Weight, etc.





위약군
Tirzepatide 1mg
Tirzepatide 5mg
Tirzepatide 10mg
Tirzepatide 15mg
활성대조군(GLP1RA)



- Active control(dulaglutide: GLP1RA) 대비 유효성에서 우월
- 고용량 Tirzepatide 군에서 dulaglutide 군 대비 높은 빈도의 부작용

Lancet 2018;392(10160):2180-2193

Nat Med 2022:28(3):450-451

Tirzepatide : Phase 2 Study – Dose Titration Study

20

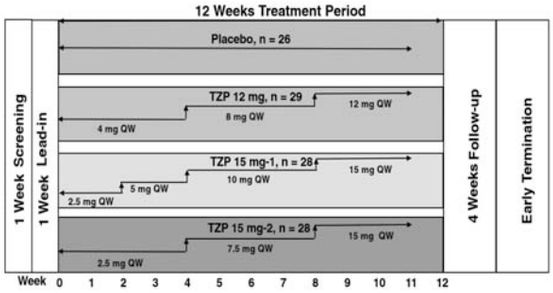
Title: A Phase 2, Double-blind, Placebo-Controlled, 3-Month Trial of LY3298176 Versus Placebo in Patients with Type 2 Diabetes Mellitus (NCT03311724)

Subject No. : 111 participants (13 sites, 1 country: United States)

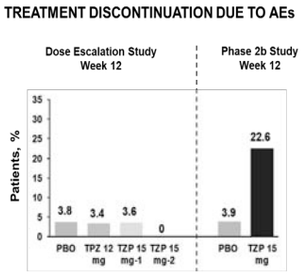
Design : Multicenter, Double-blind (Participant, Investigator), placebo-controlled, randomized, parallel-arm phase 2 titration trial

Primary Outcome : Change From Baseline in Haemoglobin A1c (HbA1c)

Secondary Outcome : Change From Baseline in Haemoglobin A1c (HbA1c



Diabetes Obes Metab 2020;22:938-946



두번째 2상 시험 첫번째 2상 시험

- Titration schedule을 조절하여 부작용의 빈도를 개선시킴
- 경쟁 제제(GLP1RA)의 안전성과 유사한 수준

→ 유효성 및 안전성 자료를 고려할 때, 제품화 가능성 높음

→ 3상 임상시험 진행

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Tirzepatide : Phase 3 Studies

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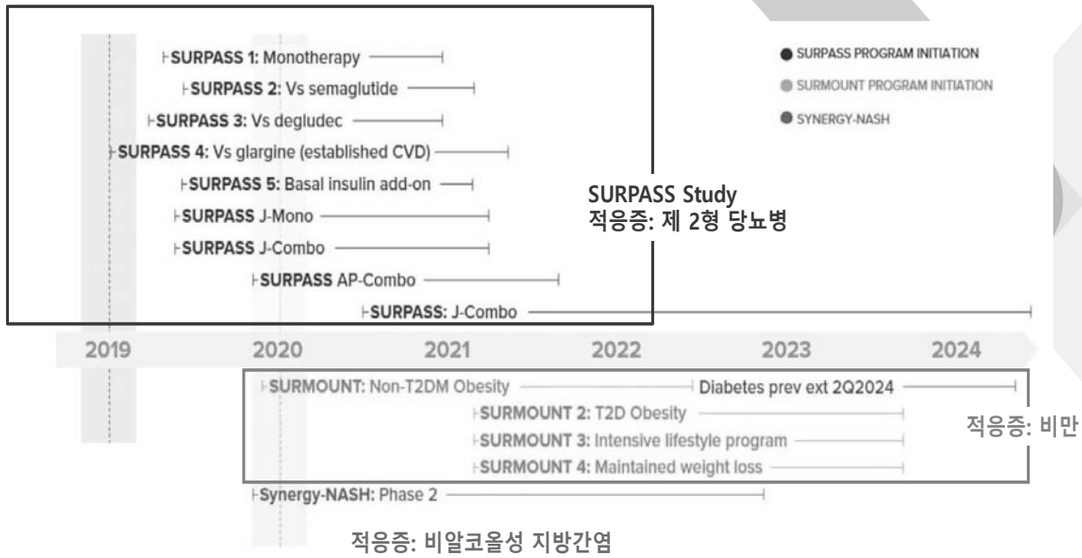

대한내분비학회 제54회 연수강좌(2022) 강의록

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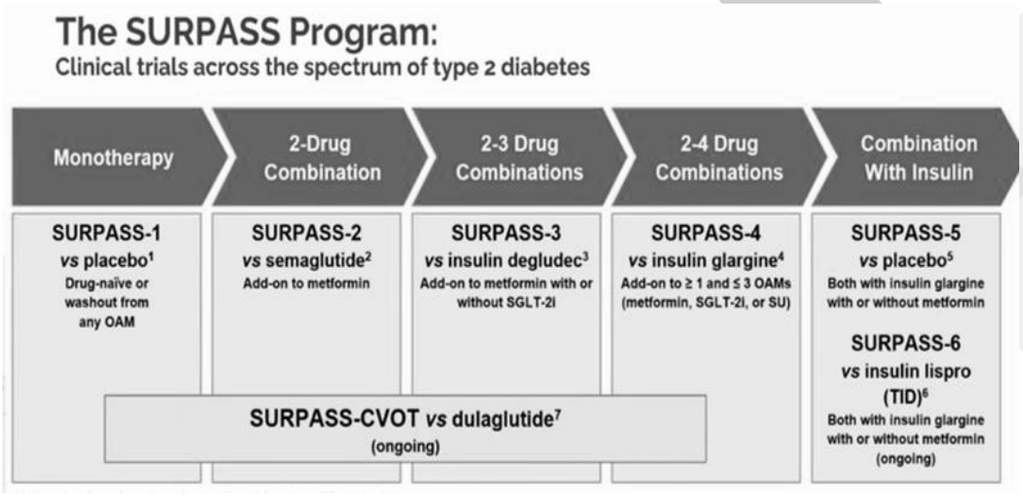
Tirzepatide : SURPASS Program

22



CVOT: cardiovascular outcome trial

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Tirzepatide : Efficacy Data

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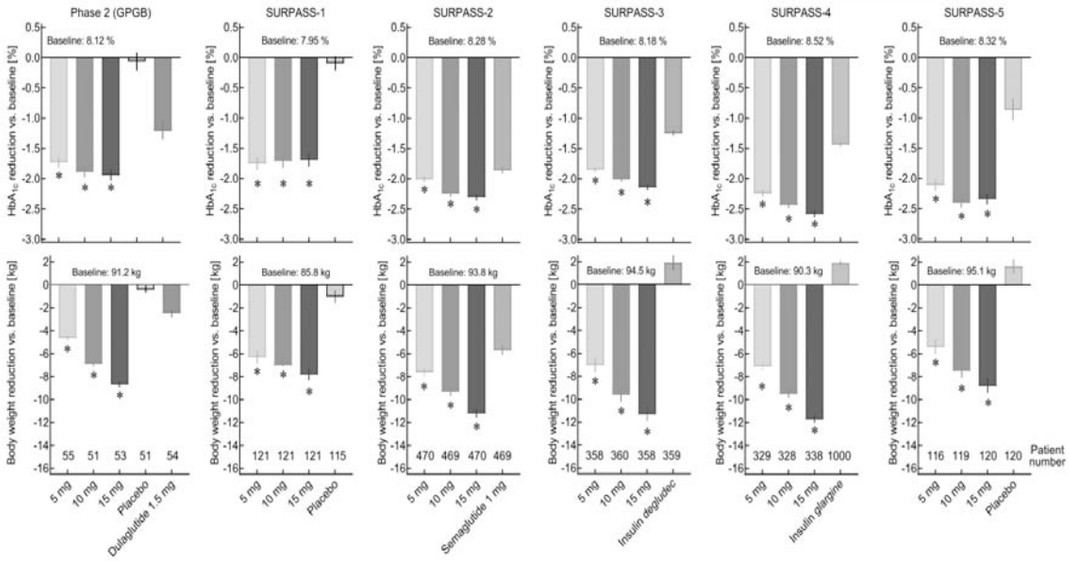

Cardiovascular Diabetology 2022;21:169

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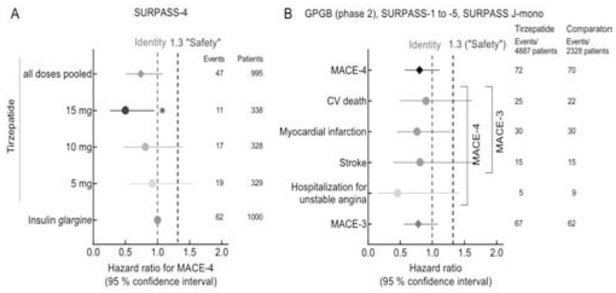
Tirzepatide : Safety Database



Cardiovascular Diabetology 2022;21:169
Tirzepatide NDA review data

Safety set 근거	9개의 P2/P3
Size of Safety Database	
IP 노출 대상자 수	7,769
시험약 노출 대상자 수	5,415
시험약 노출 patient-years	4,833
P3 시험약 노출 대상자 수	5,119
P3 52W 이상 시험약 노출	2,375
P3 78W 이상 시험약 노출	535
P3 104W 이상 시험약 노출	17
P3 patient-years(Pys)	4,721
Patient Characteristics	
eGFR<60	405
established CV disease	1,213
65세 초과	1,600

- Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes
- 당뇨병 신약의 심혈관질환에 대한 안전성을 확인하기 위한 Safety Database 확보 필요
  - ✓ 충분한 수의 시험대상자 및 충분한 추적관찰 기간 확보
  - ✓ 말기신부전, 기존 심혈관질환이 있는 대상자, 고령의 대상자에 대한 안전성 정보 필요

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Tirzepatide : New Drug Application(NDA)

CLINICAL REVIEW

Application Type	505(b)(1) New Drug Application (NDA)
Application Number(s)	NDA 215866
Priority or Standard	Priority
Submit Date(s)	September 15, 2021
Received Date(s)	September 15, 2021
PDUFA Goal Date	May 15, 2022
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Reviewer Name(s)	Frank Pucino, PharmD, MPH
Review Completion Date	May 6, 2022
Established/Proper Name	Tirzepatide
Trade Name	Mounjaro
Applicant	Eli Lilly and Company (Lilly)
Dosage Form(s)	Injection 2.5 mg/0.5 mL in a single-dose pen Injection 5 mg/0.5 mL in a single-dose pen Injection 7.5 mg/0.5 mL in a single-dose pen Injection 10 mg/0.5 mL in a single-dose pen Injection 12.5 mg/0.5 mL in a single-dose pen Injection 15 mg/0.5 mL in a single-dose pen
Applicant Proposed Dosing Regimen(s)	The recommended initiating dosage of tirzepatide is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage of tirzepatide is 15 mg injected subcutaneously once weekly.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	**Approval.** In accordance with 21CFR314.126, the Applicant has provided substantial evidence of effectiveness for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

NDA submission : 2021.09.15

Final approval : 2022.03.15

Indication: Type 2 Diabetes Mellitus

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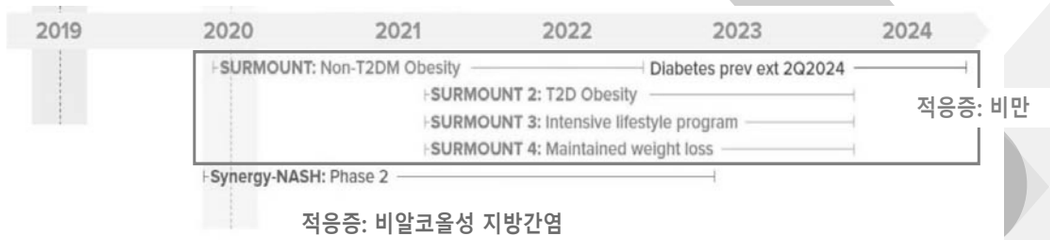
Tirzepatide : 적응증 확장 (비만, 비알코올성 지방간염)



Tirzepatide Ongoing studies

SURMOUNT 1(NCT04184622) – Obesity population, without T2DM, 72W

SURMOUNT 2(NCT04657003) – Obesity population with T2DM, 72W

SURMOUNT 3(NCT04657016) – on Intensive Lifestyle Program, without T2DM, 72W

SURMOUNT 4(NCT04660643) – Maintenance, without T2DM, 88W

대한내분비학회 제54회 연수강좌(2022) 강의록

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03
목표 제품 특성

Target Product Profile(TPP)란 무엇인가

28

- **Target product profile(TPP), 목표제품특성**
  - ✓ 개발하고자 하는 제품에 대한 총체적인 정보
  - ✓ Targeted or intended profile a pharmaceutical/biotechnology product or technology
- **TPP 가 제공하는 요소들**
  - ✓ 개발하고자 하는 제품의 특성: product's desired characteristics
  - ✓ 제품의 가치 평가를 결정하는 항목, Clinical unmet needs 극복 가능성
  - ✓ 경쟁 제품 대비 특장점, 경쟁 우위 요소 및 시장 제품 가능성
  - ➔ Summarizes intended **drug label**
- **TPP의 용도**
  - ✓ 제품 개발 계획 수립을 위한 지침으로 활용
  - ✓ Communication 수단으로 활용: 규제기관, other pharmaceutical sponsors, investigators etc

Pharmaceutical Medicine and Translational Clinical Research Chapter 5. TPP and CDP

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Target Product Profile(TPP)가 필요한 시기

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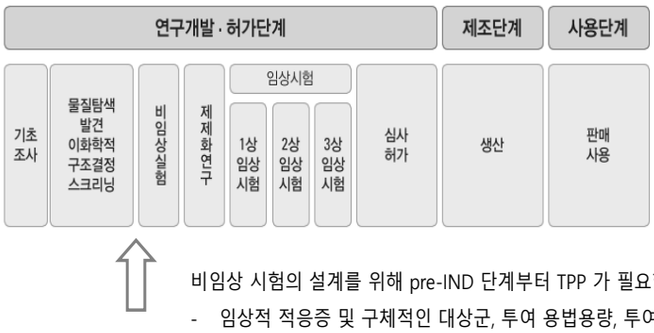
- 신약개발 전반에 걸쳐 활용됨: Pre-IND phase to post-marketing phase
- Begin with the end in mind



비임상 시험의 설계를 위해 pre-IND 단계부터 TPP 가 필요함.

- 임상적 적응증 및 구체적인 대상군, 투여 용법용량, 투여 기간, 평가방법 등의 전반적인 임상 설계를 반영한 비임상 시험 설계가 필요
- 제품의 가치평가에 도움을 줄 수 있는 요소 고려 필요

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Target Product Profile(TPP)의 구성

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- Indication and usage
- Dosage and administration
- Dosage form and strengths
- Contraindications
- Warnings and precautions
- Adverse reactions
- Drug interactions
- Use in special populations
- Drug abuse and dependence
- Over-dose
- Description
- Clinical pharmacology
- Non-clinical toxicology
- Clinical studies
- References
- How supplied/Storage& Handling
- Patient counseling information
- Others...

⇩

Drug Label

TPP guidance by US FDA, 2007

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Label 구성요소: FDA

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

MOUNJARO™ (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

INDICATIONS AND USAGE

MOUNJARO™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis (1, 5.2)
- Is not indicated for use in patients with type 1 diabetes mellitus (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1)
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15 mg subcutaneously once weekly (2.1).
- Administer once weekly at any time of day, with or without meals. (2.2)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- Rotate injection sites with each dose.

DOSAGE FORMS AND STRENGTHS

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1)
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (4, 5.4)

WARNINGS AND PRECAUTIONS

- *Pancreatitis*: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.2)
- *Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin*: Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. (5.3)
- *Hypersensitivity Reactions*: Hypersensitivity reactions have been reported. Discontinue MOUNJARO if suspected. (5.4)
- *Acute Kidney Injury*: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *Severe Gastrointestinal Disease*: Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.6)
- *Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy*: Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.7)
- *Acute Gallbladder Disease*: Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated. (5.8)

ADVERSE REACTIONS

The most common adverse reactions, reported in ≥5% of patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

MOUNJARO delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy*: Based on animal study, may cause fetal harm. (8.1)
- *Females of Reproductive Potential*: Advise females using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (7.2, 8.3, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 05/2022

AIMS BioScience

Label 구성요소: FDA (예: Tirzepatide)

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- Boxed warning
  - ✓ 경고

WARNING: RISK OF THYROID C-CELL TUMORS

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- **Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

- Indication and usage
  - ✓ 적응증(대상질환)에 대한 구체적인 설명
  - ✓ 사용이 제한되는 경우(limitations of use)

---------- INDICATIONS AND USAGE ----------

MOUNJARO™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

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AIMS BioScience

Label 구성요소: FDA (예: Tirzepatide)

33

- Dosage and administration
  - ✓ 용법용량
  - ✓ 투여 경로: 정맥주사, 피하주사, 근육주사, 국소투여 등
  - ✓ 사용량, 사용시간(식전, 식후, 식간 등), 사용 횟수

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1)
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15 mg subcutaneously once weekly (2.1).
- Administer once weekly at any time of day, with or without meals. (2.2)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- Rotate injection sites with each dose.

- Dosage forms and strengths
  - ✓ 제품 형태 및 용량

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)

AIMS BioScience

Label 구성요소: FDA (예: Tirzepatide)

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- Contraindications
  - ✓ 투여 금기
- Warnings and precautions
  - ✓ 경고 및 주의

CONTRAINDICATIONS

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- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (4, 5.4)

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- *Hypersensitivity Reactions:* Hypersensitivity reactions have been reported. Discontinue MOUNJARO if suspected. (5.4)
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *Severe Gastrointestinal Disease:* Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.6)

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Label 구성요소: FDA (예: Tirzepatide)

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- Adverse reactions
  - ✓ 이상반응
- Drug interactions
  - ✓ 상호작용
- Use in specific populations
  - ✓ 특수한 집단에서의 사용
  - ✓ 임부, 수유부, 가임여성, 신생아, 유아, 소아, 고령자

ADVERSE REACTIONS

The most common adverse reactions, reported in ≥5% of patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Based on animal study, may cause fetal harm. (8.1)
- *Females of Reproductive Potential:* Advise females using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (7.2, 8.3, 12.3)

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Label 구성요소: FDA (예: Tirzepatide)

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FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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Label 구성요소: MFDS(국내)

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- 효능효과
- 용법용량
- 사용상의 주의 사항
  1. 경고
  2. 다음 환자에는 투여하지 말 것
  3. 다음 환자에는 신중히 투여할 것
  4. 이상반응
  5. 일반적인 주의
  6. 상호작용
  7. 임부, 수유부, 가임여성, 신생아, 유아, 소아, 고령자에 대한 투여
  8. 임상검사치에의 영향
  9. 과량투여시의 처치
  10. 적용상의 주의
  11. 보관 및 취급상의 주의사항
  12. 전문가를 위한 정보
  13. 기타

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TPP의 활용

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Dynamic multidisciplinary strategic development process tool

- 제품 개발 계획 수립을 위한 지침
- 비임상 계획 수립 – 임상 설계를 고려한 비임상 계획 수립 필요
- 임상개발 계획 수립 – 임상시험에 대한 계획
- 제품 허가 전략 수립
- 개발 전주기 관리, 생산 및 마케팅 전략을 위한 정보 제공
- 기타 pharmaceutical sponsors, 연구자 및 투자자들과의 대화 수단
- 규제기관과의 communication tool 로 활용
- Label/Prescribing information 에 반영

⇨ 제품 성공을 위한 이정표


news1

[인터뷰] "TPP 없는 K-바이오 신약 개발…눈 감고 운전하는 격"

입력 2022.09.29. 오전 5:50 · 수정 2022.09.29. 오전 11:04 기사원문

김태환 기자 >

한승훈 애임스바이오 COO "K-바이오 '패스트 팔로워' 위험 수반"
"진정한 글로벌 신약 나오려면 시장 수요 맞는 포지셔닝 중요"

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TPP 개발을 위해 고려할 분야

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- Development of TPP requires cross-functional discussion between various stakeholders
  - Pharmacology
  - Metabolism & pharmacokinetics
  - Safety pharmacology & toxicology
  - Clinical pharmacology
  - Clinical development
  - Medical affairs
  - Marketing
  - Regulatory
  - Market access
  - Intellectual property
  - Strategy
  - etc

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TPP의 개발 과정

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1. 해당 질환에 대한 표준 진료 지침 확인: Review the current and possible future Standard of Care(SOC)

2. Medical unmet needs에 대한 평가

- Unmet needs in...
  - Efficacy(예: 기존 표준치료제보다 우월한 유효성을 보이는 약제 개발)
  - Safety(예: 기존 표준치료제보다 부작용이 적으면서 유효성이 유사한 약제 개발)
  - Route of administration(예: 정맥/피하로 투여하는 기존 표준치료제 → 경구 약제 개발)
  - Dosing frequency(예: 매일 투여하는 기존 표준 치료제 → 주 1회 투여하는 신약 개발)
  - Cost(예: 고비용의 기존 표준 치료제 → 비용을 낮춘 유사제제 개발)
  - Etc

3. Value proposition(가치제안) 수립 : based on the known pharmacological profile of the new drug

- Potential place in therapy(예: 1차/2차/3차 치료제 등)
- Potential economic value

4. Development program(non-clinical/clinical) 수립

Pharmaceutical Medicine and Translational Clinical Research Chapter 5. TPP and CDP

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Regulatory Perspective

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Key sections for regulatory and development team TPP

Boxed warning
Indications and usage
Dosage and administration
Dosage forms and strengths
Contraindications
Warnings and precautions
Adverse reactions
Drug interactions
Use in specific populations
Drug abuse and dependence
Overdosage
Description
Clinical pharmacology
Nonclinical toxicology
Clinical studies

Source: *FDA. Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements", http://www.fda.gov/downloads/drugs/guidances/ucm075082.pdf; 2013 [accessed 26.01.17]* [6].

- TPP summarizes the intended label

→ Efficient communication tool

→ Minimized the risk of late-stage failure in drug development process

- Drug development stage 에 따라 TPP 구성 항목과 내용이 달라질 수 있음.

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Target Product Profile: Product X				
Milestone (Meeting or Submission)	**Date**	***TPP Submitted? Y/N**	**TPP Version Date**	**TPP Discussed? Y/N**
Pre-IND IND Submission EOP1 EOP: end-of-phase EOP2A EOP2/ Pre-Phase 3 Pre-NDA/BLA Other (specify)				
Target			*Annotations*	
[This area includes the intended labeling language]			[This area includes summary information of studies (planned or completed) to support the target including protocol number, serial number, submission date, etc.]	
Comments [This area includes additional information for better clarity]				
Source: *FDA. Guidance for industry and review staff target product profile—a strategic development process tool, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf; 2007 [accessed 26.01.17[1].*				

Commercial Perspective

Contents of a commercial team TPP

Target Product Profile: Product X	
Value-proposition Target indication Target patient population Product description Dosage and route of administration	
Study design	
Efficacy	Primary endpoint Secondary endpoints
Safety	Contraindications Adverse reactions
Pricing and reimbursement Patents and exclusivities Patient share Product valuation (rNPV)	
rNPV, *Risk adjusted Net Product Value.*	

- TPP serve as a **business communication tool**
- Discussions with investors, partners, employees, physicians, payors
- Contents of regulatory TPP + assessment of commercial potential
- Market research involving Key Opinion Leaders(KOLs) and payors : define optimal profile on various parameters

TPP 고려 사항 예시 – Tirzepatide(당뇨병 약제)

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- **대상 질환**: 제1형 당뇨병 vs 제 2형 당뇨병
- **해당 질환에 대한 표준치료**
  - ✓ 급만성 당뇨합병증 예방을 위해 조기에 적극적인 병용 치료 진행
  - ✓ 다양한 계열의 당뇨병 치료제가 이미 허가됨

Table 1: Approved Therapeutic Options for the Management of Type 2 Diabetes Mellitus

Pharmacologic Class	Antihyperglycemic Drug Products
Alpha-Glucosidase Inhibitors	Acarbose; Miglitol
Amylin Mimetics	Pramlintide
Biguanides	Metformin
Bile Acid Sequestrants	Colesevelam
Dopamine-2 Agonists	Bromocriptine
DPP-4 Inhibitors	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 Receptor Agonists	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Lixisenatide, Semaglutide
Insulins and Insulin Analogues	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Premixed insulins (various)
Meglitinides	Nateglinide; Repaglinide
SGLT2 Inhibitors	Canagliflozin; Dapagliflozin; Empagliflozin, Ertugliflozin
Sulfonylureas	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
Thiazolidinediones	Pioglitazone; Rosiglitazone

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TPP 고려 사항 예시 – Tirzepatide(당뇨병 약제)

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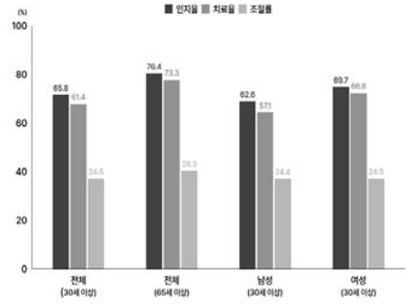
- **Medical unmet needs**
  - ✓ 다양한 계열의 당뇨병 치료제가 존재함에도 불구하고 치료 목표(HbA1c) 도달률 개선이 필요함
  - ✓ 동반 질환(비만 등) 역시 문제됨
  - ✓ GLP1RA 계열 약제는 존재하나 GIP+GLP1RA 계열은 없음

▪ Tirzepatide 특장점
최초의 GLP+GLP1RA dual agonist

당뇨병 관리 수준 (2019-2020년 통합)

당뇨병이 있는 30세 이상 성인의 65.8%만이 당뇨병이 있는 것을 알고 있고, 치료를 받는 경우는 10명 중 6명이었음.
치료 중인 경우 25%만이 당화혈색소 6.5% 미만이었음.



❖ Diabetes Factsheet in Korea 2022(대한 당뇨병학회)
: 당뇨병이 있는 환자 중 치료 목표치에 도달한 대상자가 약 25%

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TPP 고려 사항 예시 – Tirzepatide(당뇨병 약제)

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- **용량 및 투여 방법**
  - ✓ 투여경로: 피하주사제 – 자가 투약 가능하나 주사제라는 단점
  - ✓ 투여 간격 및 용량이 유사 약물 대비 경쟁력이 있는지 평가 필요(매일 주사/주1회 주사)
    - 경쟁 피하투여주사제(GLP1RA)보다 자주 투여해야하는 경우 경쟁력이 떨어짐

▪ **Tirzepatide**
주 1회 피하투여: 경쟁 제제의 투여방법 및 투여 간격과 동일

- **대조군 설정**
  - ✓ 당뇨병 치료제 임상시험의 경우, 다양한 계열 약제와의 효능 비교가 필요함
  - ✓ 위약군 설정이 필요할지? 여러 계열 약제 중 어떤 활성 대조군을 설정할 것인지?
  - ✓ 규제기관에서 필수적으로 요구하는 대조군/실험설계가 있는지 확인 필요

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TPP 고려 사항 예시 – Tirzepatide(당뇨병 약제)

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- **평가변수**
  - ✓ 당뇨병 임상시험의 일차 평가변수는 HbA1c 가 권고됨(1차 평가변수 권고가 없는 질환인 경우 추가 고민 필요)
  - ✓ 2차 평가변수 항목에 대한 고려가 필요: 약물 특이적인 기전에 따른 평가변수, 적응증 확장을 위한 평가변수 등
- **경쟁제품 대비 유효성**
  - ✓ 기존 당뇨병 치료제의 혈당 강하 효과대비 비열등~우월한 유효성 확인이 필요
  - ✓ 기타 대사적 상태(비만, 고지혈등 등)에 대한 긍정적인 효과가 있는지 탐색
- **경쟁제품 대비 안전성**
  - ✓ 기존 GLP1RA 제제의 이상반응보다 낮거나 유사한 정도의 이상반응을 보여야함(m/c: 구역구토)
- **가격 경쟁력**
  - ✓ 기존 경쟁 제품 대비 가격 경쟁력이 있는 제품 생산 가능한지 확인
- **보험급여**

▪ **Tirzepatide**
유효성: 경쟁 제제(GLP1RA) 대비 우월한 혈당 감소효과 및 체중 감소 효과
안전성: 경쟁 제제(GLP1RA)와 비슷한 정도의 이상반응 빈도
- 초기 2상에서 이상반응의 빈도가 월등히 높았으나, 용량적정기간을 최적화하여 극복함

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Take-Home Messages

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- **Target product profile(TPP, 목표제품특성)**
  - ✓ 개발하려는 제품에 대한 총체적인 정보 제공, 제품 성공을 위한 이정표, summarizes intended drug label
  - ✓ Dynamic multidisciplinary strategic development process tool
    : 개발 과정에 따라 수정/변화
    : 규제기관, 회사, 연구자 등 다양한 집단과 분야의 의견을 반영

- **TPP의 개발 과정**
  - ✓ 해당 질환에 대한 표준 진료 지침 확인
  - ✓ medical unmet needs 평가
  - ✓ 가치제안 수립
  - ✓ 비임상/임상 개발전략 수립

- **TPP는 신약 개발 전반에 걸쳐 활용됨: Begin with the end in mind**
  - ✓ 후기 단계 개발 실패 위험을 최소화, 제품 개발 시간을 단축

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임상 진입 시 고려해야할 목표 제품 특성(Target Profile Product, TPP)

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