A. PRODUCT PROFILE-1

1. Background-3

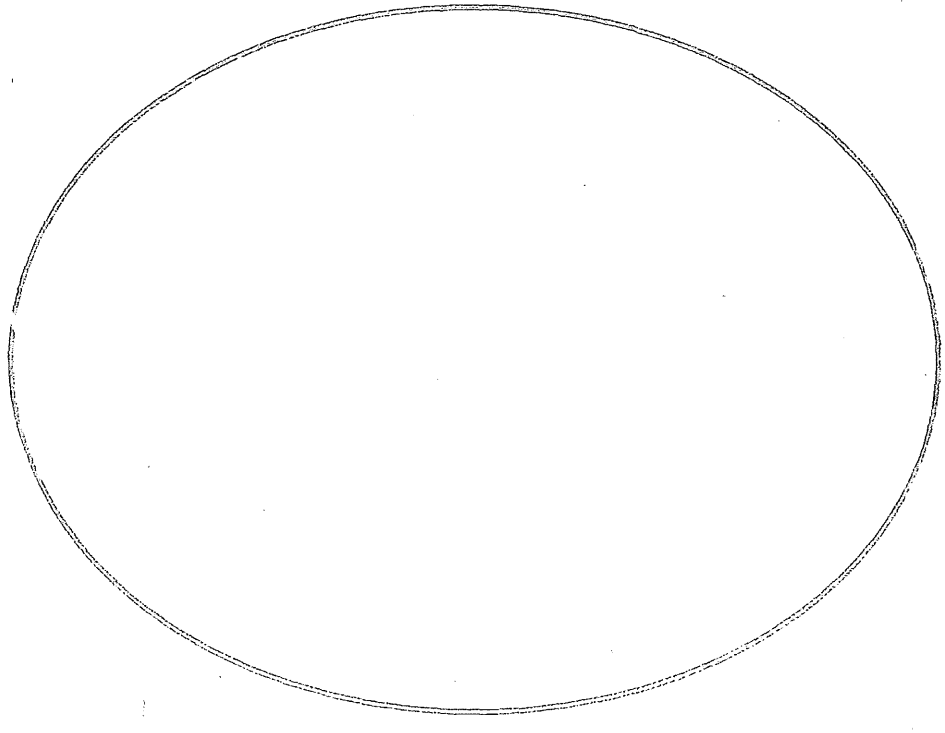
In Japan, we have been managed national surveillance committee since 2010, and have been carried out the research on natural history of patients with prion disease since 2013.

The study collects longitudinal prospective data on many patients diagnosed with or at high risk of developing prion disease, regardless of whether or not they are receiving treatment.

The aim is to build up a very detailed understanding of disease progression that can then be used to compare with patients receiving new drugs in the future.

A. PRODUCT PROFILE-2

1. Structure of "P092"



A. PRODUCT PROFILE-2

2.Scientific rationale: Pre-clinical pharmacology

- The mechanism of the action of P092 in humans is believed be associated with
- in vitro
- in vivo.
- Pharmacologic activity of P092 is
- Toxicology of P092 is

A. PRODUCT PROFILE-2

2. Scientific rationale: ADME

- The absorption of P092 is
- The distribution of P092 is
- The metabolism of P092 is
- The excretion of P092 is

B. TARGET PRODUCT PROFILE-1

3. Dosage

- Indications: Treatment of prion disease
- Formulation: Intravenous drip
- Administration ~in adults~ (Tentative):
  - dose range is ● to ▲mg/day
  - dose interval is
  - dose escalation is

  ~As dosage initial dose, ● to ▲mg is administered for ● to ▲ days.~

B. TARGET PRODUCT PROFILE-2

◆Target Product Profile

✓Safety/Tolerability:

Preclinical study demonstrates safety of P092 for rats and monkeys.

✓Non-Inferiority to other compounds

Preclinical study suggests

✓Superiority & Efficacy:

Preclinical study suggests

C. KEY TACTICAL ELEMENTS-1

Strategy:

・J-phase I should be conducted to define the positioning of P092 in Japan and to confirm the results of the pre-clinical study and also according to the recommendation of KIKO consultation.

・Utilize the information in foreign countries most efficiently for Japan complete clinical data package.
⇒Consider additional studies to construct the validity of data clinical package.

・Facilitate the speed of enrolment and quality using establishment on high performance study sites and study networks well managed by appropriate CRC and SMO.

C. KEY TACTICAL ELEMENTS-2

◆Option A: Preclinincal ⇒P Ⅰ ⇒P Ⅱ

✓Safety/Tolerability:

Preclinical study demonstrates safety of P092 for rats and monkeys.
J-phase I demonstrate the safety of P092 for human.

✓Non-Inferiority to NATURAL or other compounds

◆Option B: Preclinical ⇒P Ⅰ / Ⅱa (Single dose～Long-term)

✓Safety/Tolerability:

Preclinical study demonstrate safety of P092 for rats and monkeys.
J-phase I will demonstrate the safety of P092 for human in single-dose.

✓Superiority & Efficacy:

J-phase I demonstrates the safety and tolerability of P092 in the first dose, and the efficacy in long-term study.

D. DEVELOPMENT ISSUE (NON-CLINICAL) - 1

1. Nonclinical Pharmacology
   Absence of raw data and safety pharmacology studies(S7A&B)

2. Nonclinical Toxicology
   Luck of raw data, GLP records and TK and recovery studies

3. Pharmaceutical Science
   No issues

4. Nonclinical ADME
   No issues

5. Clinical Pharmacology / Population Pharmacokinetics
   No issues

D. DEVELOPMENT ISSUE (NON-CLINICAL) - 2

6. Statistical
   Sample size power: The accuracy for estimation can not be high, because response data for P092 is not enough.

7. Regulatory
   - Need to construct the strong rationale about the complete clinical data package for J-NDS (the reason why we don't have the Japanese and foreign data except for the data from the research on natural history)
   - Need to produce CTD as NDA dossier based on Gaiyo draft (No experience in Gihu Univ. or TMDU)

8. Marketing
   Not identified

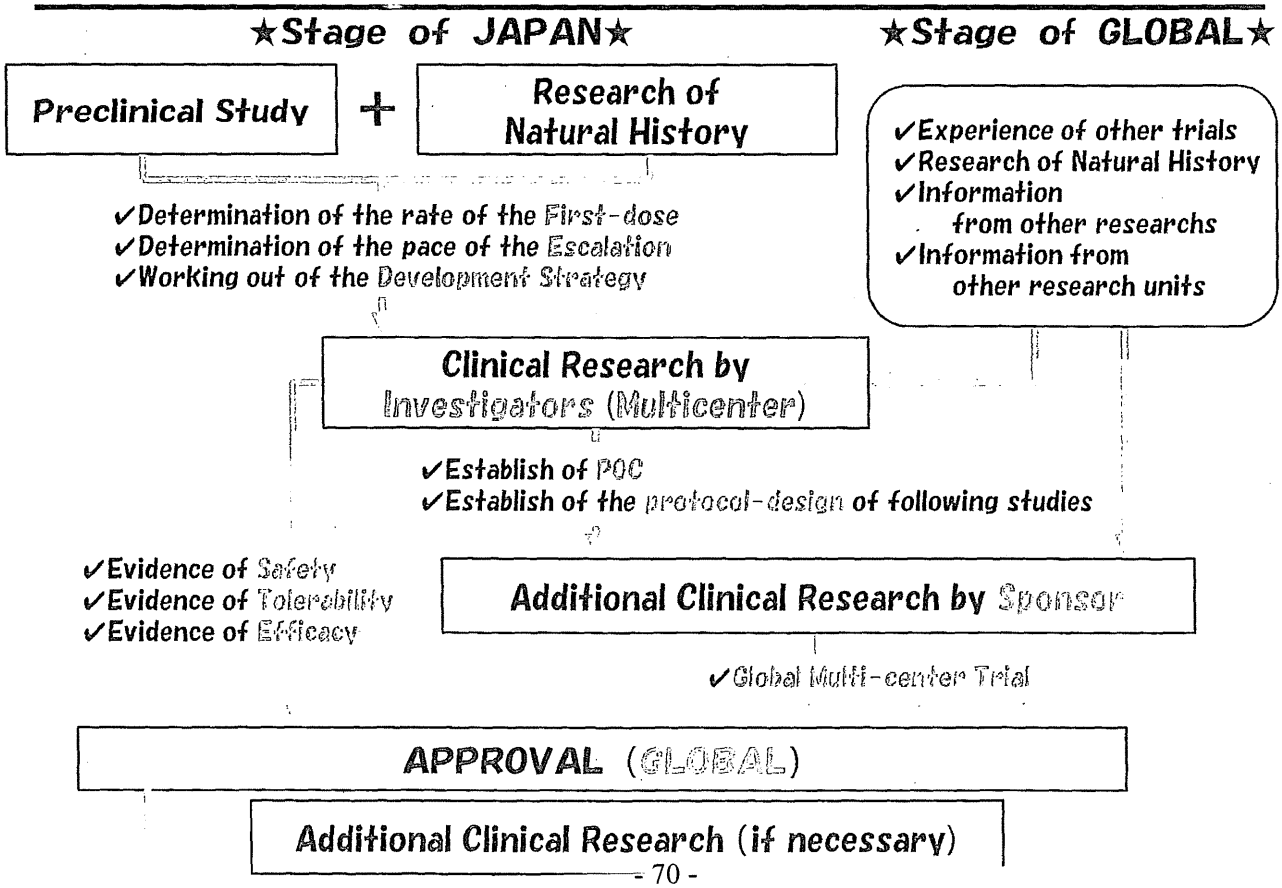
D. DEVELOPMENT ISSUE (CLINICAL)

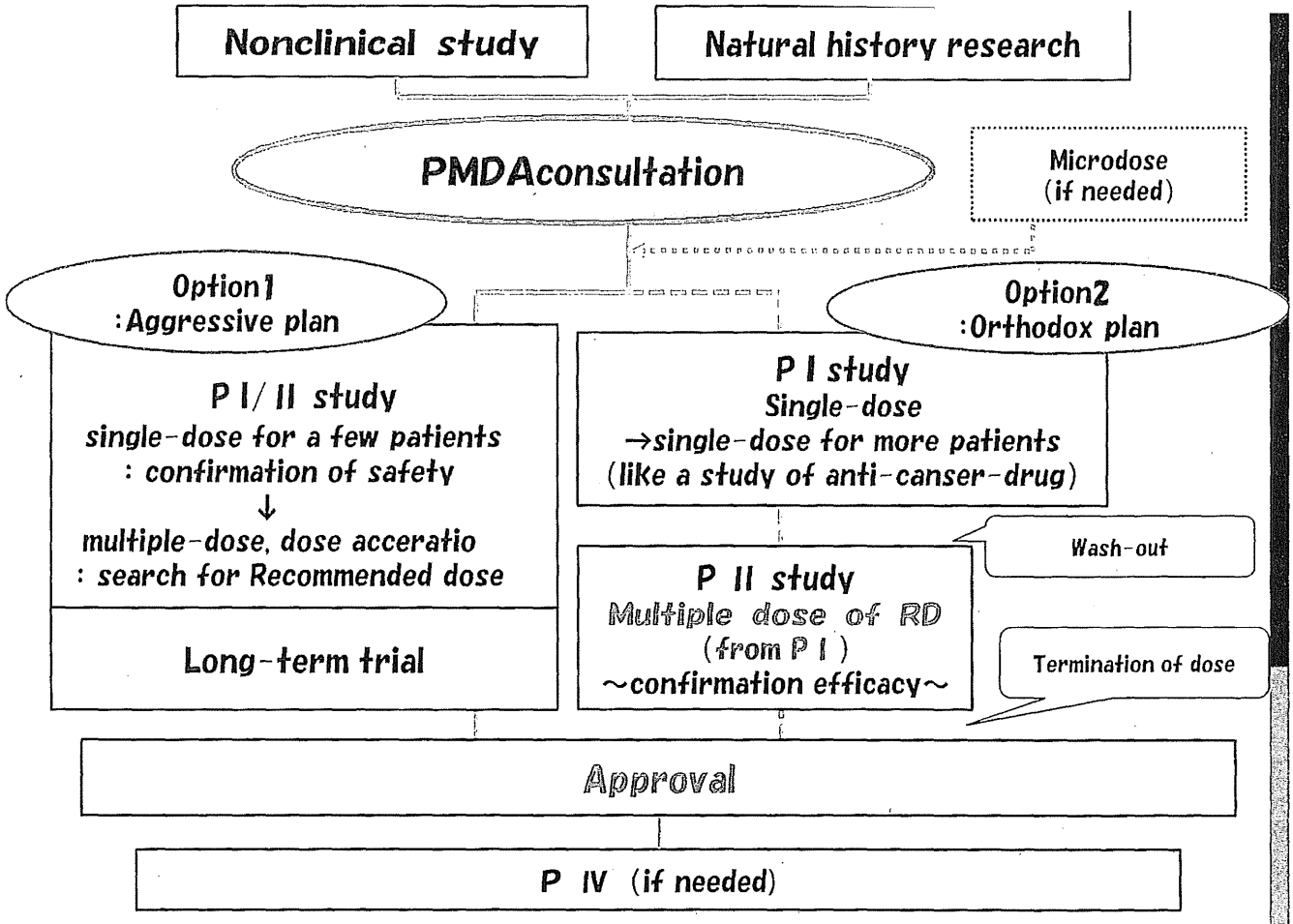
6. Reasons for the determination rate of the first dose

7. Period of discontinue dosing for patients
   - less number of patients
   - Patients have poor prognosis thereafter therapies
   - Discontinuing of dosing will have medical risks and ethical problem.

8. Marketing
   Not identified

E. LOGIC OF CLINICAL PLAN & RELATIONSHIP





F. CLINICAL DEVELOPMENT PLAN-2 (JAPAN)

【Regular Method】

◆J-phase I :

- Patients with sub-acute prion disease
- Open-label, Single dose
- Safety
- Superiority to no dose
- ● weeks of observation

⇒Need concern with the treatment of patients after termination of the phase I trial

◆Global-phase Ⅱ:

- Patients with sub-acute and acute prion disease
- Open-label, Multiple dose, Dose escalation
  Long-term trial (to patient's death)
- Safety in long-term dosing
- Superiority to low dose
- ● weeks of treatment

⇒Treatment of after termination of the phase I trial

F. CLINICAL DEVELOPMENT PLAN-3 (JAPAN)

【 Irregular Method】

◆J-phase 0: Micro dose study or Exploratory IND Studies

- Patients with sub-acute and/or acute prion disease
- Open-label, Single and multiple dose,
  Dose escalation or Maintenance dose

【Micro dose study】

✓Single dose of 1/100 of Minimal effective dose (or 100μg)
✓Assess the PK / distribution of drug

【Exploratory IND Studies】

✓Starting dose: 1/50 of dosage for most sensitve animal
✓Maximum dose: 1/2 of AUC at NOAEL
✓Minimal dose to onset pharmacologic action

- Treatment from initiation to patient's death
  ⇒ No concern with the treatment of patients
  after termination of the phase I trial

★ We need prove the safety in Human-use of P092 before the clinical trial.

F. CLINICAL DEVELOPMENT PLAN-3 (JAPAN)

【 Irregular Method】

◆J-phase I / II a:

- Patients with sub-acute and/or acute prion disease
- Open-label, Single and multiple dose,
  Dose escalation or Maintenance dose
  Long-term trial (to patient's death)
- Safety
  Superiority to no dose and low dose
- Treatment from initiation to patient's death
  ⇒ No concern with the treatment of patients
  after termination of the phase I trial

◆Gloal PhaseIV (if required)

- Patients with sevral type prion disease
- Open-label, Long-term
- Safety in long-term dose

G. ISSUES & PLANS FOR RESOLUTION (JAPAN)

～Potential risks associated with the J-CDP and Challenge～

◆ Lack of getting active comparator

1) The Research of Natural History
   - Increasing study sites might increase inter-site variation and protocol violation.
   - Set up high performance study sites well managed CRC and study networks well managed SMOs.
   - Already started negotiation with potential high performance investigators

2) Collection of the Foreign Findings and Achievements
   - More cases prion disease in UK and US.
   - More experiments of research and trials in UK, US and other Europe countries.
   - Validated method of researches.
   - Have examined more patients than Japan (in the UK and US)

G. ISSUES & PLANS FOR RESOLUTION (JAPAN)

Potential risks associated with the J-CDP and Challenge

◆ Delay of CRF collection
   - Less number of patients

⇒Increasing study sites

   - Less number of investigators of Prion disease (Human Resource)

⇒"Visit type CRF" or another method (eg. Remote data entry system)
⇒Establish the Remote data entry system with UMIN

◆ Facilitate the timeline from Unblinding to NDS
⇒Front-loading of the preparation for all parts pf CTD/CSRs except the phase Ⅲ study before the unblinding.

H. GO/NO GO CRITERIA FOR EACH MILESTONE

◆ Go / No-Go decision criteria for proceeding to filing will depend on the result of

- Safety/Tolerability in the single dose
- Non-inferiority to natural condition
- Superiority to natural condition and to low dose (●●mg or lower dose)

I. CRITICAL PATH ACTIVITIES : PROJECT SCHEDULE

J. PRE-KIKO CONSULTATION

We had pre-NDS KIKO consultation to determine the validity of NDA strategy on

- The validity of extrapolating the foreign data into the Japanese NDA submission
- Validity of the Complete Clinical Data Package
- The appropriateness of the recommended Dosage and Administration section of the draft labeling.

KIKO will accept the strategy of extrapolation or recommen us to conduct Phase I/ II a study in Japan.

K. KIKO CONCLUSIONS

- That study has demonstrated that Omg/day is an effective dose for Japanese prion desease patients.
- There is uncertainly of the value of Omg and Omg per day.
- There are insufficient safety or efficacy data to approve.
- PK/PD will be affected by ethnic difference in their characteristics.

L. OTHER KIKO COMMENTS

◇ Because they believed that we would not accept their comments, they have shared the Gaiyo and their review of it with PMDA who agree with their view.

◇ P092 should be developed in Japan and that only the Phase Ⅱ study was additionally required to confirm the results of phase I study and also to define the positioning of P092 in Japan.

◇ That they would not comment on the validity of the complete clinical data package because their opinion was that we should return for review of this completing the confirmatory Phase I study.

N. THE COUNTER MEASURE TO ACHIEVE THE FASTEST TIMELINE FOR NDS WITH SUCCESS

◆ For the enrollment

- Well trained CRCs in all sites (or principle site) with well organized by appropriate SMOs.
- Increasing the number of sites.
  "Super performance sites"
- Facilitate symptoms of prion disease
  - using the scale
- Encouraging voluntary efforts by financial firms
- Sophisticated advertisement
  - WEB
  - throughout the member of JACOP

O. THE COUNTER MEASURE TO ACHIEVE THE FASTEST TIMELINE FOR NDS WITH *SUCCESS*

◆ For the timeline from the LPO to the unblinding
- Front-loading the clean up for CRFs using 'Visit type CRF' with 'Visit by visit Collection to reduce remainding CRFs after LPO.

◆ For the timeline from unblinding to NDS
- Front-loading of the preparation for all parts of CTD/CSRs expert the phase III study before the unblinding
- To skip pre-NDS KIKO consultation

P. RISKS FOR THE COUNTER MEASURE WE PROPOSED

◆ The possibility of unfavorable results
- Unexpected high response with P092
- Increasing variability of outcome due to increasing the sites
- Decrease power due to decreased the number of target patients

◆ The possibility of failure to shorten the timeline
- Difficulty of the production for very low dose formulation to definite the efficacy of P092
- Inexperience for orphan drug development by academia
- The possibility of delay of approval for our strategy of NDS
- No negotiation for the data package before NDS due to skip pre-NDS KIKO consultation

★ＦＩＨ試験に必要な非臨床試験の種類★

1）　安全性薬理試験
2）　トキシコキネティックス・薬物動態試験
3）　単回投与毒性試験（２種以上）
4）　反復投与毒性試験（２種以上）
5）　遺伝毒性試験
6）　がん原性試験
7）　生殖発生毒性試験

※3）6）7）については、ヒト試験開始時には不要

1）安全性薬理試験

ヒト初回投与前には，主要な生理的機能（例えば，心血管系，中枢神経系及び呼吸器系）に及ぼす機能的な影響を明らかにすべきである（ICH S7A, S7B, S6及び M3（R2）ガイドライン参照）、また、必要に応じて他の器官系への影響を検討するための追加試験を実施する。

2）トキシコキネティックス・薬物動態試験

相同タンパク、遺伝子改変動物、あるいはヒト細胞等を用いたin vitro試験により、被験薬の安全性評価に資する情報が得られる場合がある。ヒトタンパクあるいはヒト型タンパクは、実験動物において免疫原性を示す傾向があり、反復投与毒性試験では、中和抗体等の発現により、ヒトでの毒性学的影響を予測困難にする場合がある。
病態モデル動物では、薬理学的作用、薬物動態（PK）、疾病に関連する標的分子の発現、臨床での用法／用量及び安全性に関して有益な情報が得られることがある。このため、非臨床試験で一般的に用いられる動物種に代わって、病態モデル動物を用いた試験が利用される場合があるが、その場合、当該試験が被験薬の安全性評価に有用であることを科学的に説明すべきである。

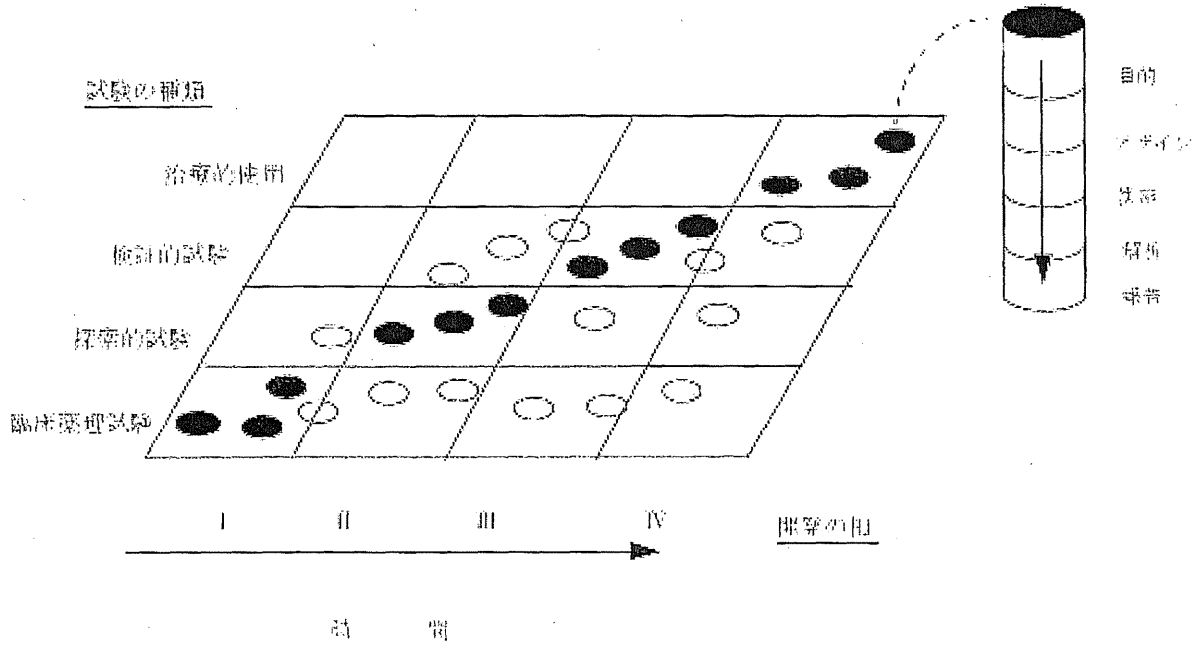
4）反復投与毒性試験（２種以上）

被験物質を哺乳動物に繰り返し投与した時に生じる毒性変化を用量及び時間との関連で把握するための試験。
２種の哺乳類（げっ歯類１種、非げっ歯類１種）で実施され、無毒性量が決定される。
用量反応性の見られる項目、標的臓器、重篤度などについても評価する。
薬物濃度（血中、組織）と毒性所見の関連性（トキシコキネティクス）は必須事項。
可逆性についての所見も重要。

5）遺伝毒性試験

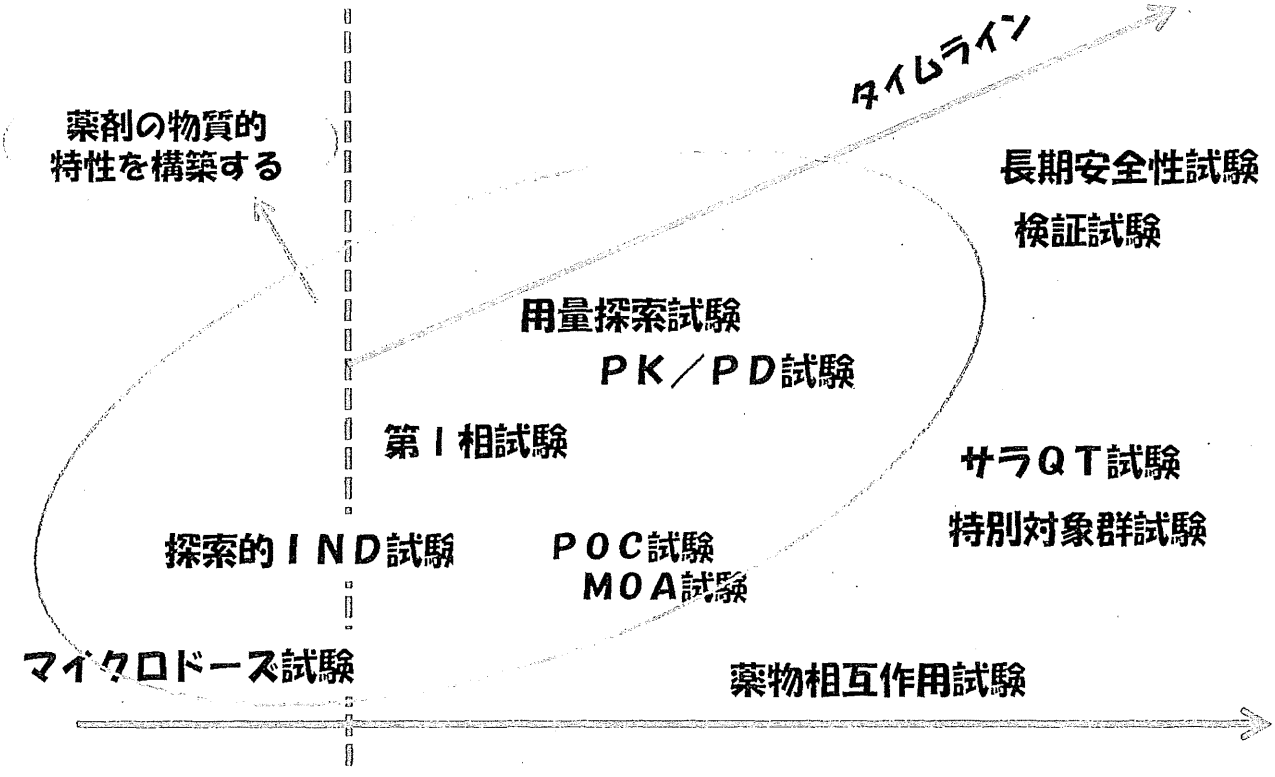
従来の細菌を用いる遺伝子突然変異試験、およびげっ歯類造血細胞を用いる染色体損傷のための in vivo 試験（小核試験）に加え、哺乳類の培養細胞を用いる染色体異常試験にマウスリンフォーマを使用する試験が追加容認された。
これらの試験ですべて陽性が出た場合、臨床試験は中止すべきとされる。

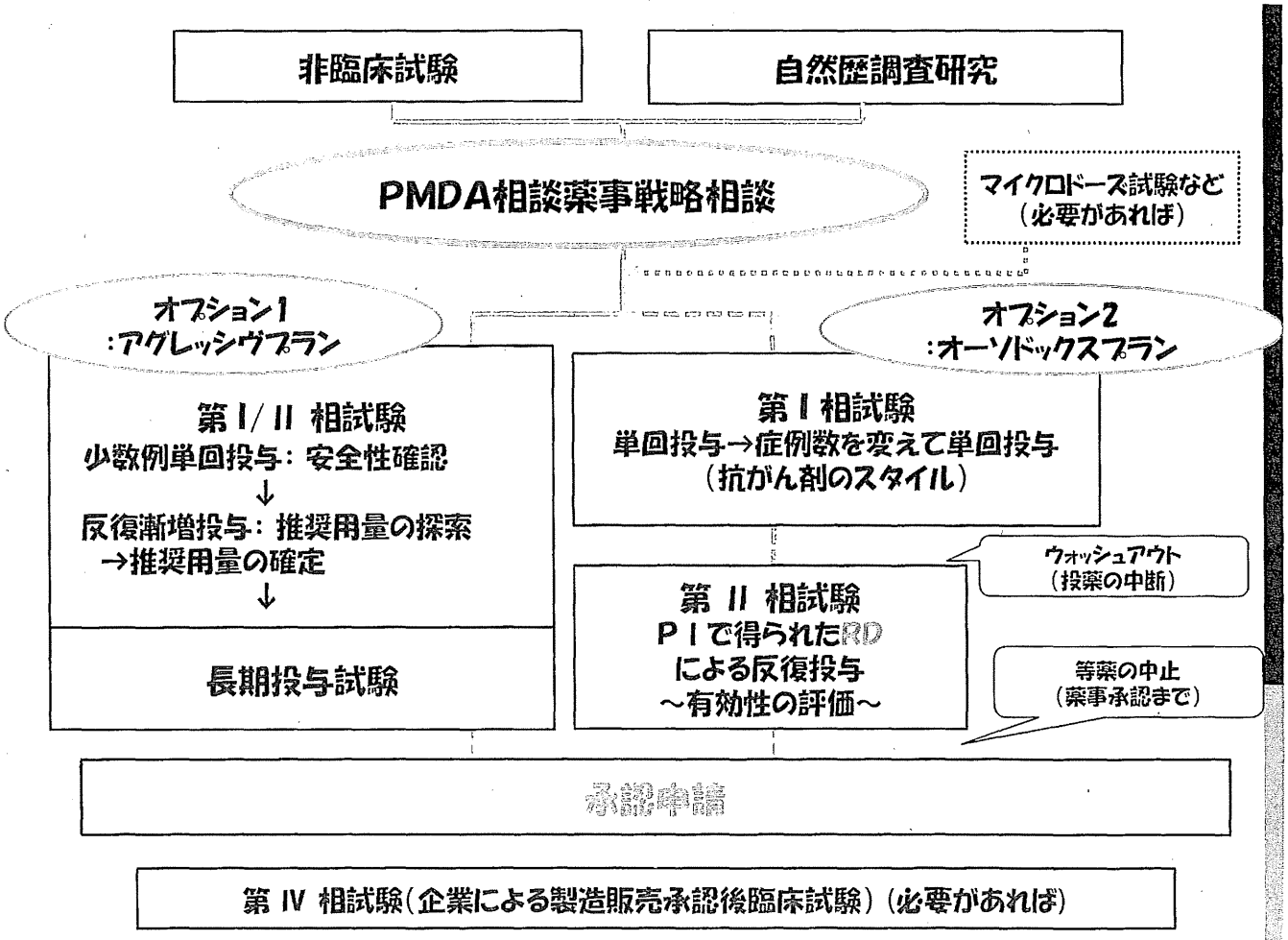
開発の相と試験の種類の関係



●：ある開発の相で最も一般的に実施される試験
○：その相で実施されることが比較的まれな試験

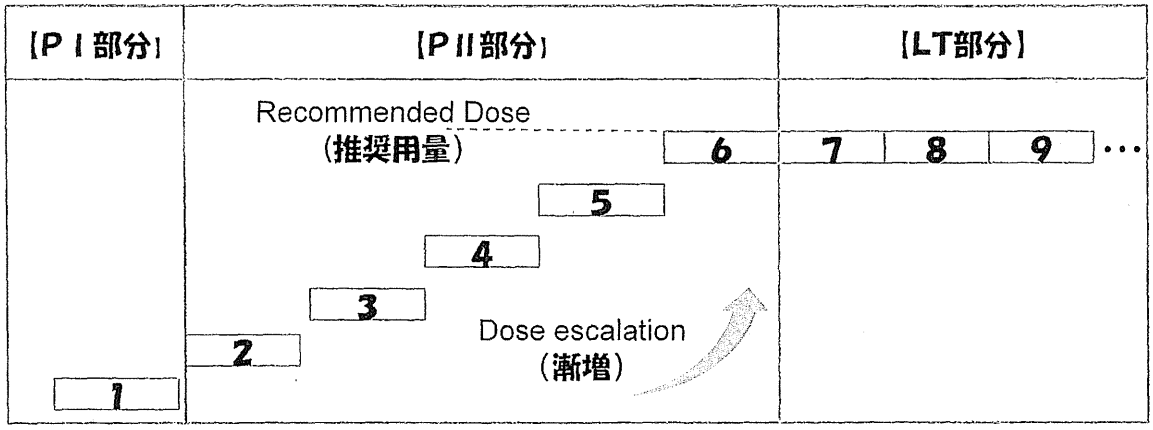
臨床試験の種類と段階


タイムライン
薬剤の物質的
特性を構築する
長期安全性試験
検証試験
用量探索試験
PK／PD試験
第Ⅰ相試験
サラQT試験
特別対象群試験
探索的IND試験
POC試験
MOA試験
マイクロドーズ試験
薬物相互作用試験


非臨床試験
自然歴調査研究
PMDA相談薬事戦略相談
マイクロドーズ試験など
（必要があれば）
オプション1
:アグレッシヴプラン
オプション2
:オーソドックスプラン
第Ⅰ/Ⅱ 相試験
少数例単回投与：安全性確認
↓
反復漸増投与：推奨用量の探索
→推奨用量の確定
↓
長期投与試験
第Ⅰ相試験
単回投与→症例数を変えて単回投与
（抗がん剤のスタイル）
第 Ⅱ 相試験
PⅠで得られたRD
による反復投与
～有効性の評価～
ウォッシュアウト
（投薬の中断）
等薬の中止
（薬事承認まで）
承認申請
第 Ⅳ 相試験（企業による製造販売承認後臨床試験）（必要があれば）

オプション1：アグレッシブプラン

✓初回投与量の単回投与にて、ヒトへの投与の安全性を確認する
✓予測推奨用量まで漸増する
✓予測推奨用量に到達した時点で、長期投与試験に移行
✓一連の試験内で安全性（急性・長期）、忍容性・有効性を確認、
推奨用量を探索・決定する



★アグレッシブプランのメリット

✓同一被験者にてウォッシュアウトの期間なく投薬・評価が可能
※代替治療がないので、治療薬の中断は倫理的に問題あり
✓個体差によるバイアスの抑制し評価できる
✓治験実施に係る審査申請などの手続きが簡略化される

★アグレッシブプランのデメリット

✓プラセボ使用したブラインドによる比較が困難
✓治験期間が（特に被験者にとって）長期になる →負担増大
✓処方量の管理などが煩雑になる
✓評価・分析が複雑になる

★アグレッシブプランにおける
初回投与量の設定と漸増ペースの設定

◆Step 1：NOAEL(No Observable AdverseEffect Level：無毒性量)の設定

◆Step 2：HED(Human Equivalent Dose：ヒト等価量)へNOAEL から換算
～一般的には体表面積で換算

◆Step 3：最適な種の選択
✓追加要因：代謝，受容体，結合エピトープ
✓既定値：最も感受性の高い動物(最低HED)

◆Step 4：安全性係数(10 倍以上)の適用
→MRSD(Maximum Recommended Starting Dose)の決定

◆Step 5：PAD(Pharmacological Active Dose：薬理学的作用量)の検討

計算式

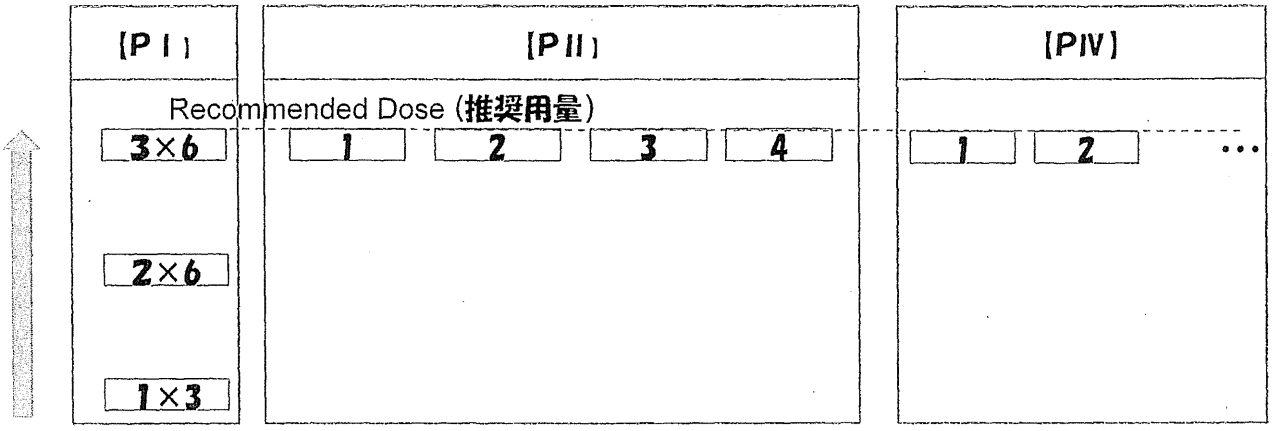
★MARBEL

計算式

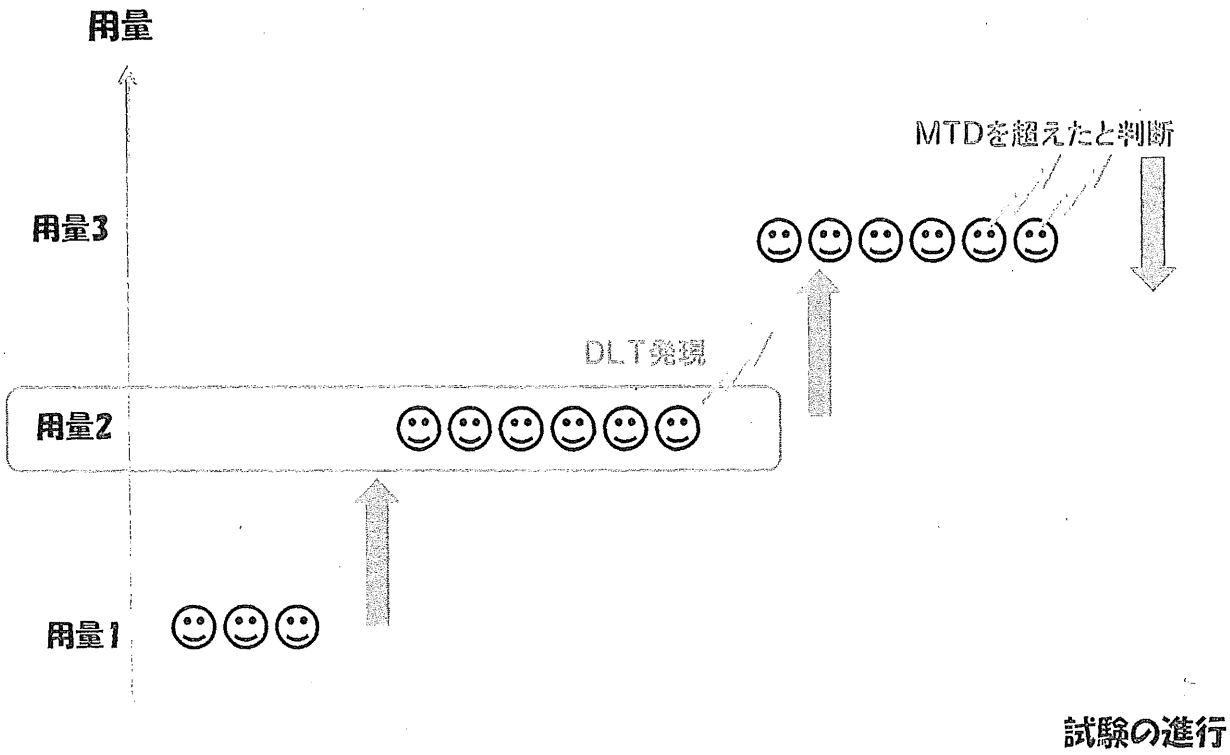
オプション2：オーソドックスプラン

✔PⅠ(用量1)にて、ヒトへの投与の安全性を確認
✔PⅠ(用量2)にて、DLT(用量制限毒性：dose limiting toxicity)の探索
✔PⅠ(用量3)にて、MTD(最大忍容量：maximum tolerated dose)の探索
✔PⅡにて、実際の治療に近い形での有効性を評価

✔PⅣにて、保留していた項目の安全性を確認



★オーソドックスプラン（ＰⅠ）での増量・減量のイメージ



★オーソドックスプランのメリット

✓試験の初めからプラセボ使用したブラインドによる比較が可能
　→より客観的・科学的な評価が可能
✓より短期間での試験実施及び評価が可能
✓各段階での処方量の管理などがシンプル
✓各被験者における治験参加機関が短い

★オーソドックスプランのデメリット

✓個体差によるバイアスの抑制し評価が困難
✓各フェーズの間隙で投薬の不可
　・ウォッシュアウトの必要
　・未承認薬の処方の不可
✓治験実施に係る手続き、報告手続きがアグレッシブプランに比べ煩雑