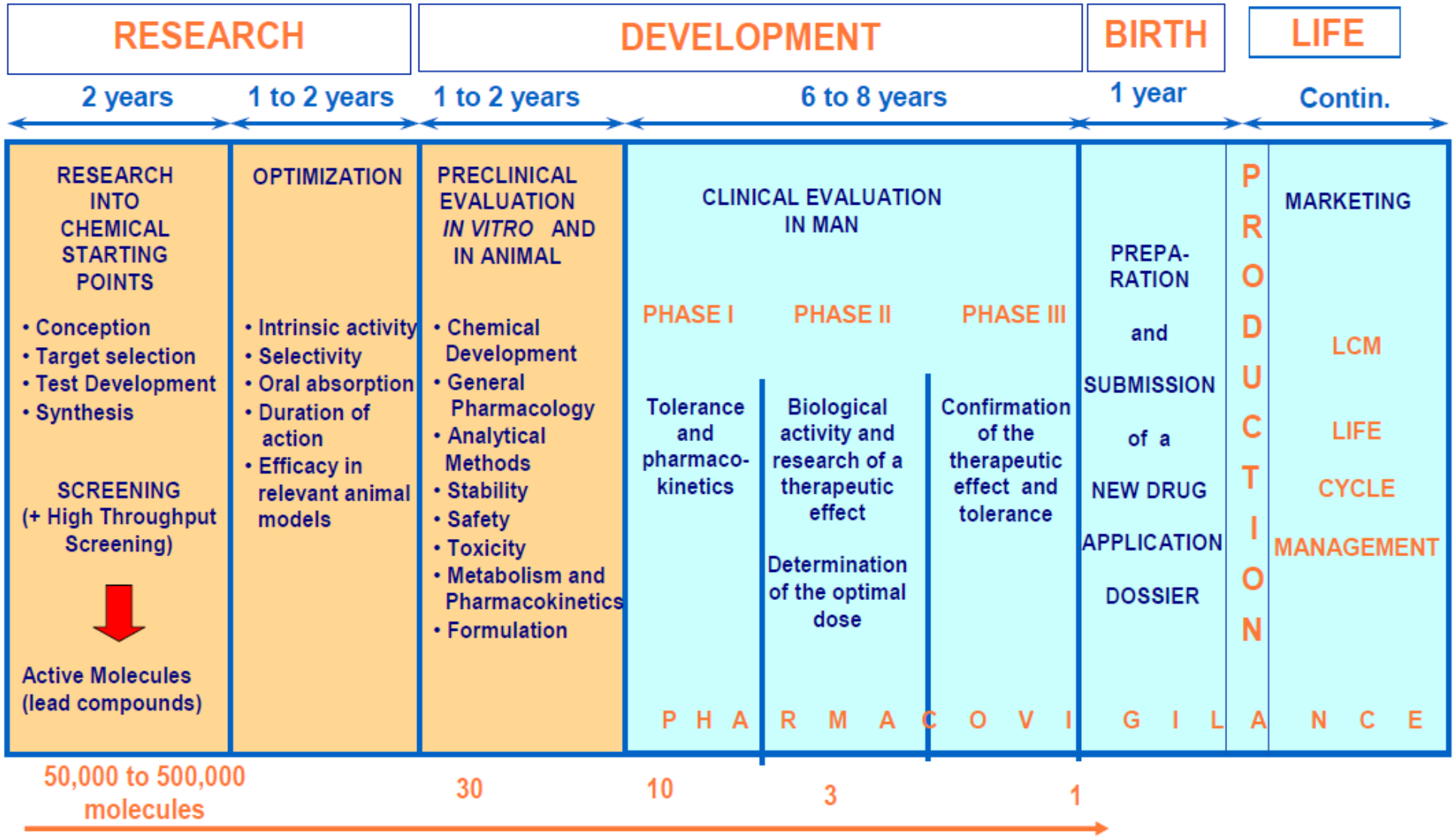
Essais de phase II

Dr Edouard-Jules LAFORGUE

Phases de développement du médicament



Phases de développement du médicament

Nombre de produits par étape pour **arriver à 1 médicament sur le marché** (estimations) :

- 1 000 molécules synthétisées
- 100 testées chez l'animal
- <10 testées chez l'homme
- **1 médicament qui obtient l'AMM**

Phases de développement du médicament

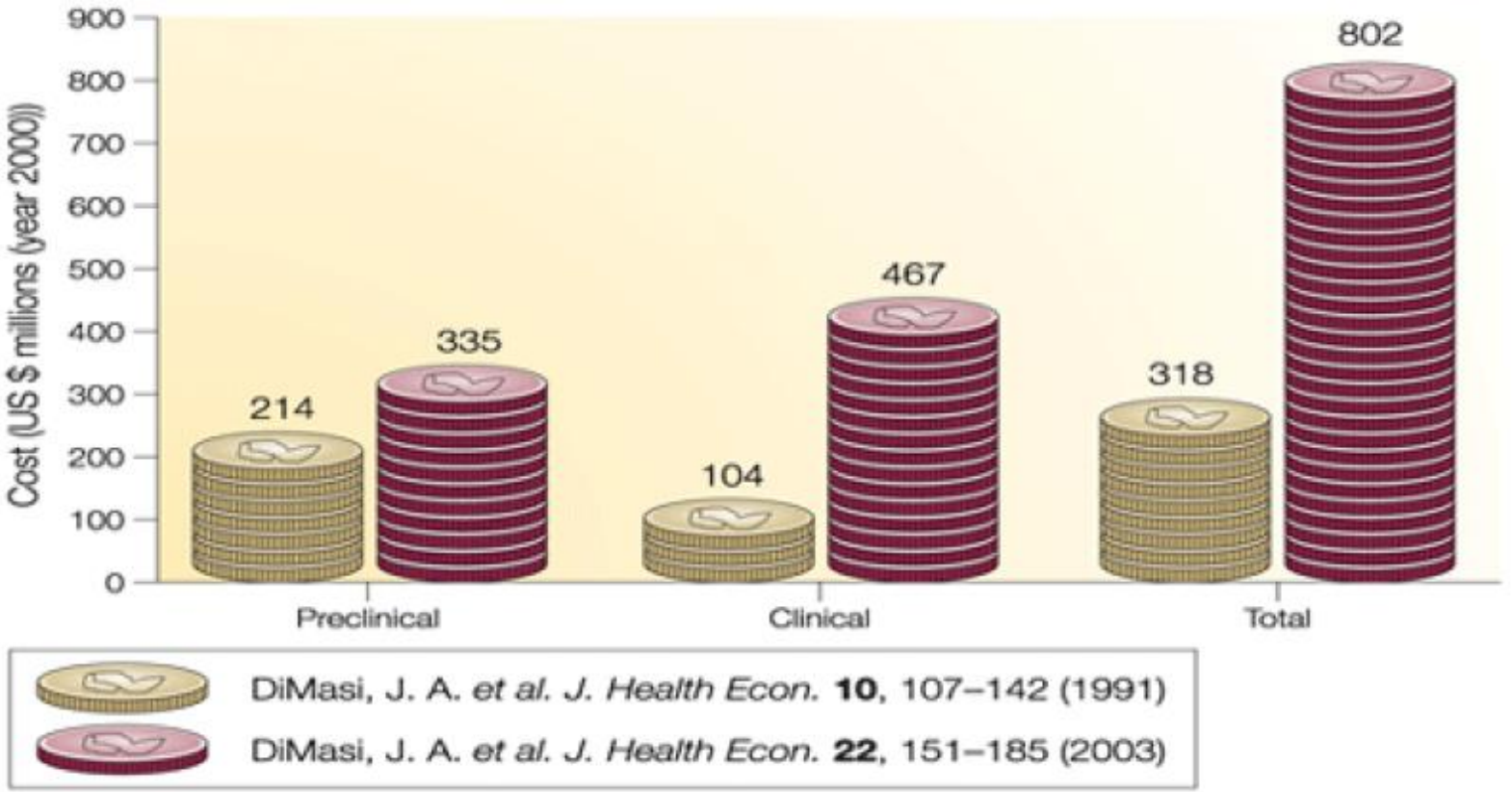
Phases	Objectifs généraux
I	Tolérance, pharmacocinétique, pharmacodynamie (±) chez le volontaire sain (sauf produits onco ou facteurs de croissance…)
IIa IIb	Tolérance, activité, efficacité (±) chez les patients (sous-groupe de la population cible) Détermination de la relation dose-effet chez les patients
III	Evaluation (confirmation) de l'efficacité thérapeutique et de la tolérance, contre produit de référence (si disponible), à large échelle dans population cible
IIIb, IV	Etudes post-marketing (tolérance, extensions d'indications ou autres populations, demandes réglementaires…)

Phases de développement du médicament

Estimation des **coûts de développement d'un nouveau produit** jusqu'à la mise sur le marché (million $1997) (d'après : Updating the Cost of a New Chemical Entity by Dr. Hannah Kettler, Office of Health Economics)

Study	Years	Total Capitalised Costs
Hansen, 1979	1963-75	**138**
Wiggins, 1987	1963-75	**156**
DiMasi et. al., 1991	1970-82	**312**
OTA, 1993	1970-82	**431**
Myers and Howe, 1997	1970-82	**459**
DiMasi et. al., 2003		**800**

Phases de développement du médicament



Raisons de l’arrêt de développement

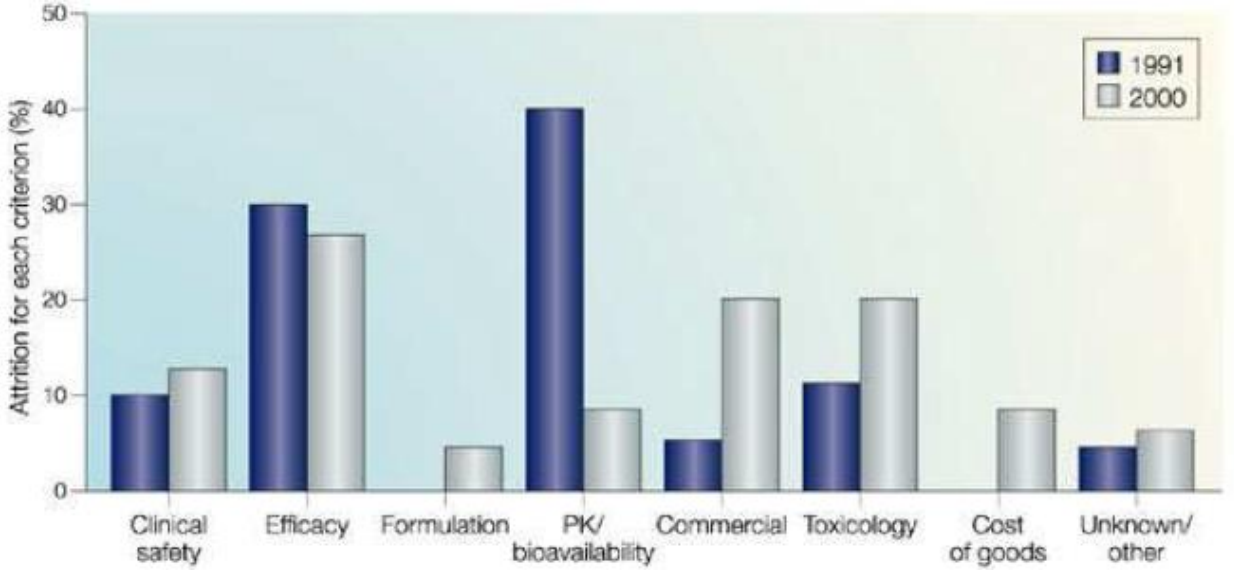
Forte **régulation de l’industrie pharmaceutique**
Médicaments en R&D: de 5930 (98) à 7406 (06)

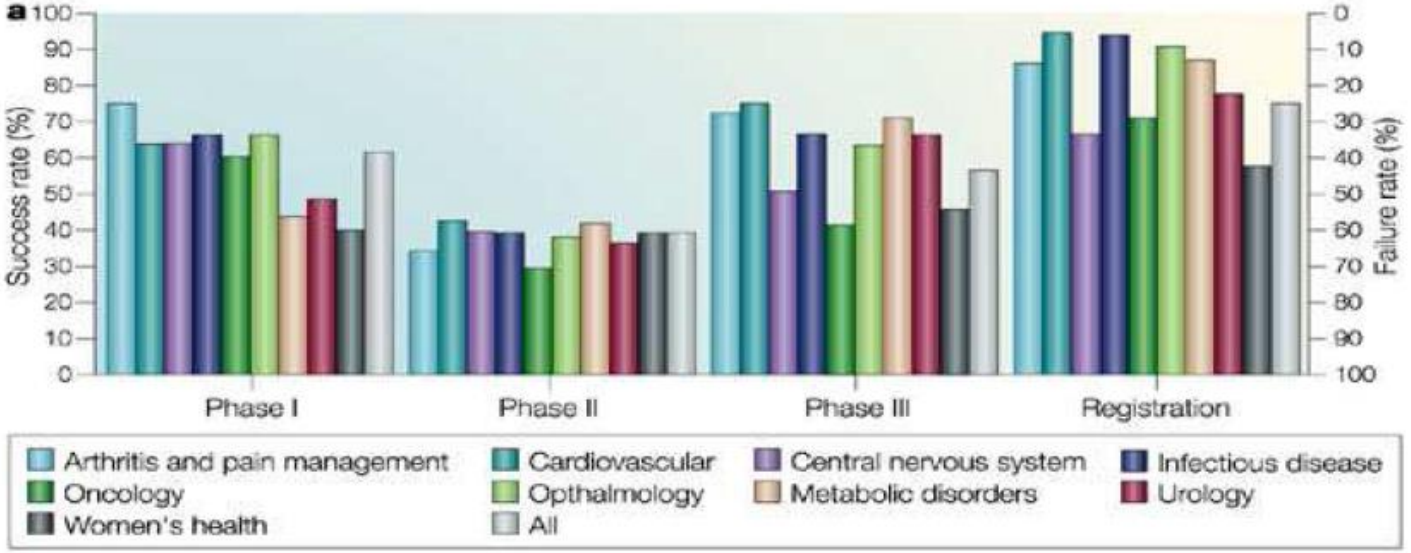
Raisons de l’arrêt:

- 22 % toxicité
- 31 % efficacité
- 41 % propriété physicochimiques
- 6 % marketing

% élevé de d’arrêt de développement:

- 38 % en phase I
- 60 % en phase II
- 40 % en phase III
- 23 % à l’autorisation





Phases II

- Estimation du **taux de réponse** (efficacité) d'une dose fixe

- Etablir la **dose optimale**, meilleur effet thérapeutique avec le minimum d'effets indésirables

- Petit nombre de malade

- Non comparatifs (IIa)
- Comparatifs (IIb)

Phases II

- Durée: 1 à 3 ans (durée courte)
- **Première administration chez le malade**
- Pharmacodynamie/efficacité/mécanisme d'action
- Objectif: détermination des doses utilisées en Phase III

Phases II

Phase IIa

- Chez quelques patients rigoureusement sélectionnés
- Preuve de concept pharmacologique chez le patient (population cible)

Phase IIb

- Choix de la fourchette de doses avec un bon bénéfice/risque
- Confirmation du potentiel « médicament »

Les études de phase IIa : l'exemple

Exemple de méthodologie

REL-1017 (Esmethadone) as Adjunctive Treatment in Patients With Major Depressive Disorder: A Phase 2a Randomized Double-Blind Trial

Maurizio Fava, M.D., Stephen Stahl, M.D., Luca Pani, M.D., Sara De Martin, Pharm.D., Marco Pappagallo, M.D., Clotilde Guidetti, M.D., Andrea Alimonti, M.D., Ezio Bettini, Ph.D., Richard M. Mangano, Ph.D., Thomas Wessel, M.D., Marc de Somer, M.D., Judy Caron, Ph.D., Ottavio V. Vitolo, M.D., Gina R. DiGuglielmo, B.S., Adam Gilbert, M.P.H., Hiren Mehta, Ph.D., Morgan Kearney, M.D., Andrea Mattarei, Ph.D., Marco Gentilucci, M.D., Franco Folli, M.D., Sergio Traversa, Pharm.D., Charles E. Inturrisi, Ph.D., Paolo L. Manfredi, M.D.

Exemple de méthodologie

Objective: The purpose of this study was to examine the effects of REL-1017 (esmethadone), a novel *N*-methyl-D-aspartate receptor (NMDAR) channel blocker, in patients with major depressive disorder who failed to benefit from one to three standard antidepressant treatments in their current major depressive episode.

Methods: A 7-day phase 2 multicenter randomized double-blind placebo-controlled trial, comprising three arms, was conducted to assess the safety, tolerability, pharmacokinetics, and efficacy of two dosages of REL-1017 (25 mg or 50 mg orally once a day). Patients were randomly assigned in a 1:1:1 ratio to placebo (N=22), REL-1017 25 mg/day (N=19), or REL-1017 50 mg/day (N=21). Safety scales included the 4-item Positive Symptom Rating Scale for psychotomimetic symptoms, the Clinician-Administered Dissociative States Scale for dissociative symptoms, the Clinical Opiate Withdrawal Scale for withdrawal signs and symptoms, and the Columbia-Suicide Severity Rating Scale for suicidality. The primary efficacy endpoint was the Montgomery-Åsberg Depression Scale (MADRS) score. All 62 randomly assigned patients were included in the full analysis set population analysis.

Exemple de méthodologie

TABLE 1. Baseline demographic and clinical characteristics of patients with major depressive disorder in the safety analysis set[a]

Characteristic	Placebo (N=22)		REL-1017 25 mg (N=19)		REL-1017 50 mg (N=21)		All Patients (N=62)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)[b]	49.7	11.1	49.4	12.4	48.6	10.9	49.2	11.3
	N	%	N	%	N	%	N	%
Sex								
Male	11	50.0	11	57.9	12	57.1	34	54.8
Female	11	50.0	8	42.1	9	42.9	28	45.2
Ethnicity								
Hispanic or Latino	1	4.5	1	5.3	0	0.0	2	3.2
Not Hispanic or Latino	21	95.5	18	94.7	21	100.0	60	96.8
Race								
Asian	0	0	0	0	1	4.8	1	1.6
Black or African American	13	59.1	13	68.4	13	61.9	39	62.9
Caucasian	9	40.9	6	31.6	7	33.3	22	35.5
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Body mass index[c]	29.02	4.27	27.66	3.33	27.66	5.00	28.15	4.26
Baseline HAM-D score	25.6	3.5	25.1	3.5	25.0	3.8	25.3	3.6

[a] Percentages were calculated on the basis of the number of nonmissing records (patients) in each variable per treatment arm and overall. HAM-D=17-item Hamilton Depression Rating Scale.

[b] Data are for age at the time of informed consent. The age ranges for the placebo group, REL-1017 25-mg group, REL-1017 50-mg group, and all patients were 22–63 years, 22–64 years, 27–62 years, and 22–64 years, respectively.

[c] For body mass index, the ranges for the placebo group, REL-1017 25-mg group, REL-1017 50-mg group, and all patients were 21.2–34.9, 22.7–34.6, 18.6–34.8, and 18.6–34.9, respectively.

Exemple de méthodologie

TABLE 2. Treatment-emergent adverse events by preferred term in patients with major depressive disorder in the safety analysis set[a]

	Placebo (N=23)		REL-1017 25 mg (N=19)		REL-1017 50 mg (N=21)		All Patients (N=62)	
Variable	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patients with a serious adverse event	0	0.0	0	0.0	0	0.0	0	0.0
Patients with a severe treatment-emergent adverse event	0	0.0	0	0.0	0	0.0	0	0.0
Patients with at least one adverse event	12	54.5	9	47.4	15	71.4	36	58.1
Treatment-emergent adverse events occurring in three or more patients								
Constipation	3	13.6	1	5.3	3	14.3	7	11.3
Nausea	2	9.1	1	5.3	2	9.5	5	8.1
Diarrhea	3	13.6	0	0.0	0	0.0	3	4.8
Headache	3	13.6	2	10.5	3	14.3	8	12.9
Somnolence	2	9.1	1	5.3	1	4.8	4	6.5
Dizziness	1	4.5	1	5.3	1	4.8	3	4.8
Back pain	0	0.0	1	5.3	2	9.5	3	4.8

Exemple de méthodologie

TABLE 3. Efficacy assessment at day 7 (end of dosing period, postdose) and day 14 (end of observation period) in patients with major depressive disorder in the full analysis set population[a]

Measure, Time Point, and Group	N	Least Square Mean[b]	SE	Difference of Least Square Mean Drug Versus Placebo[c]	90% CI	Effect Size[d]	p[e]
MADRS							
Day 7							
Placebo	21	−8.7	2.3				
REL-1017 25 mg	19	−17.4	2.5	−8.7	−14.3, −3.1	0.8	0.0122
REL-1017 50 mg	21	−15.9	2.4	−7.2	−12.7, −1.8	0.7	0.0308
Day 14							
Placebo	20	−7.4	2.4				
REL-1017 25 mg	16	−16.8	2.7	−9.4	−15.4, −3.5	0.9	0.0103
REL-1017 50 mg	18	−17.8	2.6	−10.4	−16.1, −4.6	1.0	0.0039

Exemple de méthodologie

TABLE 3. Efficacy assessment at day 7 (end of dosing period, postdose) and day 14 (end of observation period) in patients with major depressive disorder in the full analysis set population[a]

Measure, Time Point, and Group	N	Least Square Mean[b]	SE	Difference of Least Square Mean Drug Versus Placebo[c]	90% CI	Effect Size[d]	p[e]
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Placebo	21	−8.7	2.3				
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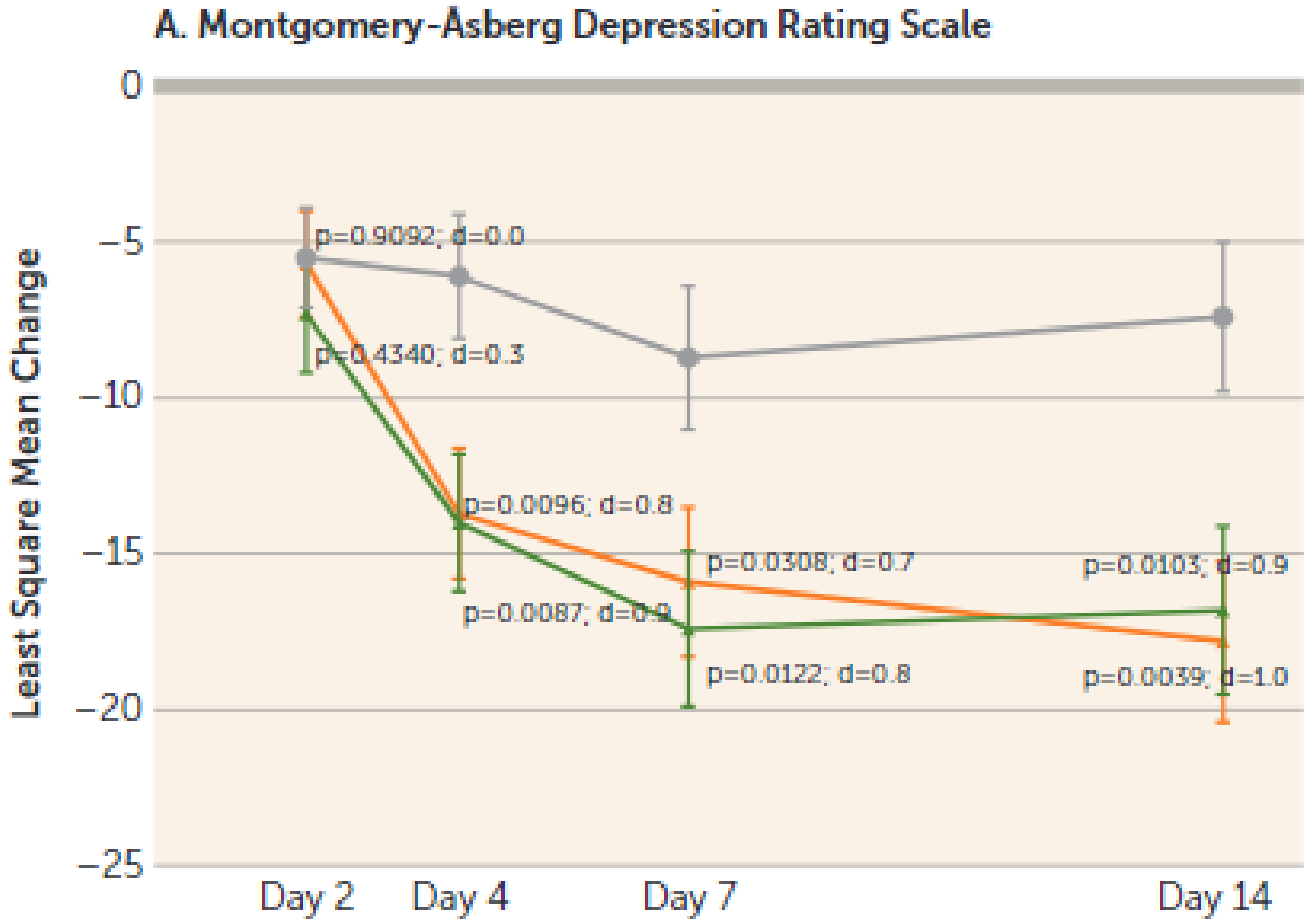
REL-1017 50 mg	21	−15.9	2.4	−7.2	−12.7, −1.8	0.7	0.0308
Day 14							
Placebo	20	−7.4	2.4				
REL-1017 25 mg	16	−16.8	2.7	−9.4	−15.4, −3.5	0.9	0.0103
REL-1017 50 mg	18	−17.8	2.6	−10.4	−16.1, −4.6	1.0	0.0039

Exemple de méthodologie

FIGURE 2. Efficacy endpoints in patients receiving placebo (N=22), REL-1017 25 mg/day (N=19), or REL-1017 50 mg/day (N=21)[a]



Exemple de méthodologie

Results: Patients experienced mild or moderate transient adverse events and no evidence of dissociative or psychotomimetic effects, opioid effects, or withdrawal signs and symptoms. The improvement in MADRS score shown on day 4 in both of the REL-1017 dosage groups was sustained through day 7 (last dose) and day 14 (7 days after the last dose), with effect sizes from 0.7 to 1.0.

Exemple de méthodologie

Vos conclusions ?

Exemple de méthodologie

Conclusions: This trial showed favorable safety, tolerability, and pharmacokinetic profiles and suggests that REL-1017 may have rapid and sustained antidepressant effects compared with placebo in patients with inadequate responses to antidepressant treatments. These results will need confirmation in larger and longer trials.

Les études de phase IIa

Bridging studies

- **Confirmer la bonne tolérance chez les patients**
- Etude pour confirmer l'efficacité ou la tolérance sur des **populations particulières** (obèses, IR, sujets âgés, ethnies, …)

Proof of concept

- Preuve de concept
- Ce n'est **pas une étude pivot**
- Nombre limité de sujets sélectionnés
- Peu de doses différentes testées
- Efficacité évaluée sur des biomarqueurs notamment
- **Pas toujours de groupe contrôle**

Possibilité de passer en étude pivot (phase IIb)

Les études de phase IIa

Choix des doses : déterminées sur les résultats des 1ères études (critères : tolérance, activité, pharmacocinétique)

Choix du nombre de doses : plus réduit / phase 1 (études plus lourdes)

Choix de la durée de traitement : fonction de la pathologie, suffisante pour montrer une activité, éventuellement limitée par la durée des études de toxicité

Les études de phase IIa

Essais non comparatifs (Ethique et statistique)

- **Minimiser le nombre de patients** inclus
- Comparaison à un **taux d'efficacité de référence**
- **Etape non définitive**

Les études de phase IIa

Biais:

- **Effet Hawthorne**: savoir que l'on participe à une expérience augmente la motivation
- **Effet placebo**
- **Régression à la moyenne**

Pour confirmer l'efficacité thérapeutique: nécessité d'un groupe contrôle… Passage en phase IIb/III

Les études de phase IIb : l'exemple

Exemple de méthodologie

RESEARCH Open Access

Efficacy and safety of fixed doses of intranasal Esketamine as an add-on therapy to Oral antidepressants in Japanese patients with treatment-resistant depression: a phase 2b randomized clinical study

Nagahide Takahashi[1], Aya Yamada[2], Ayako Shiraishi[2], Hiroko Shimizu[2], Ryosuke Goto[2] and Yushin Tominaga[2*]

Exemple de méthodologie

Methods: This Phase 2b, randomized, double-blind (DB), placebo-controlled study was conducted in adult Japanese patients with TRD meeting the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) criteria of major depressive disorder with nonresponse to ≥ 1 but < 5 different ADs in the current episode at screening. Patients were treated with a new oral AD for 6 weeks (prospective lead-in phase); nonresponders were randomized (2:1:1:1) to placebo or esketamine (28-, 56-, or 84-mg) nasal spray along with the continued use of AD for 4 weeks (DB induction phase). Responders (≥50% reduction from baseline in the Montgomery-Asberg Depression Rating Scale [MADRS] total score) from the DB induction phase continued into the 24-week posttreatment phase and patients who relapsed could participate in a 4-week open-label (OL) second induction (flexibly-dosed esketamine). The primary efficacy endpoint, change from baseline in the MADRS total score at Day 28 in the DB induction phase, was based on mixed-effects model using repeated measures pairwise comparisons using a Dunnett adjustment.

Exemple de méthodologie

Table 1 Demographics and Baseline Characteristics

Category	Esk28 (*N* = 41)	Esk56 (*N* = 40)	Esk84 (*N* = 41)	Placebo (*N* = 80)	Total (*N* = 202)
Age (years)					
Mean (SD)	45.9 (9.97)	42.5 (8.36)	41.9 (10.26)	43.3 (11.40)	43.4 (10.35)
Sex, n (%)					
Male	18 (43.9%)	24 (60.0%)	23 (56.1%)	41 (51.3%)	106 (52.5%)
Female	23 (56.1%)	16 (40.0%)	18 (43.9%)	39 (48.8%)	96 (47.5%)
Baseline BMI (kg/m^2)					
Mean (SD)	25.81 (4.733)	24.37 (5.388)	23.86 (3.949)	25.01 (4.729)	24.81 (4.735)
Hypertension status[a], n (%)					
Yes	5 (12.2%)	11 (27.5%)	9 (22.0%)	10 (12.5%)	35 (17.3%)
No	36 (87.8%)	29 (72.5%)	32 (78.0%)	70 (87.5%)	167 (82.7%)
Oral antidepressant, n (%)					
Duloxetine	1 (2.4%)	4 (10.0%)	4 (9.8%)	11 (13.8%)	20 (9.9%)
Venlafaxine XR	9 (22.0%)	7 (17.5%)	4 (9.8%)	10 (12.5%)	30 (14.9%)
Escitalopram	18 (43.9%)	11 (27.5%)	17 (41.5%)	25 (31.3%)	71 (35.1%)
Sertraline	8 (19.5%)	11 (27.5%)	10 (24.4%)	23 (28.8%)	52 (25.7%)
Paroxetine CR	2 (4.9%)	6 (15.0%)	1 (2.4%)	5 (6.3%)	14 (6.9%)
Mirtazapine	3 (7.3%)	1 (2.5%)	5 (12.2%)	6 (7.5%)	15 (7.4%)
Age when diagnosed with MDD (years)					
Mean (SD)	37.9 (10.80)	33.5 (9.51)	32.8 (9.76)	34.4 (11.18)	34.6 (10.58)

[a]Hypertension status = Yes, if SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg at least one time point before DB Induction Phase. Hypertension status = No, if SBP < 140 mmHg and DBP < 90 mmHg at all time points before the DB Induction Phase

Abbreviations: *BMI* body mass index, *CR* controlled-release, *DB* double-blind, *DBP* diastolic blood pressure, *Esk* esketamine, *MDD* major depressive disorder, *N* number of patients, *n* subset of patients, *SBP* systolic blood pressure, *SD* standard deviation, *XR* extended-release

Exemple de méthodologie

Table 3 MADRS Total Score: Change From Baseline to Day 28 MMRM; DB Induction Phase

Category	Esk28 (*N* = 41)	Esk56 (*N* = 40)	Esk84 (*N* = 41)	Placebo (*N* = 80)
Baseline				
N	41	40	41	80
Mean (SD)	38.4 (6.07)	37.9 (5.41)	35.9 (5.28)	37.7 (5.65)
Median (Range)	36.0 (28; 58)	37.5 (29; 49)	35.0 (28; 47)	37.0 (29; 51)
Day 28				
N	39	34	39	72
Mean (SD)	22.9 (12.46)	23.6 (11.01)	21.0 (11.24)	22.4 (11.43)
Median (Range)	24.0 (0; 55)	22.0 (2; 47)	19.0 (1; 43)	21.5 (1; 46)
Change from baseline to Day 28 (DB)				
N	39	34	39	72
Mean (SD)	- 15.2 (13.07)	- 14.5 (10.53)	- 15.1 (12.21)	- 15.3 (11.68)
Median (Range)	- 13.0 (– 52; 7)	- 15.0 (– 40; 5)	- 15.0 (– 44; 5)	- 13.0 (– 50; 4)

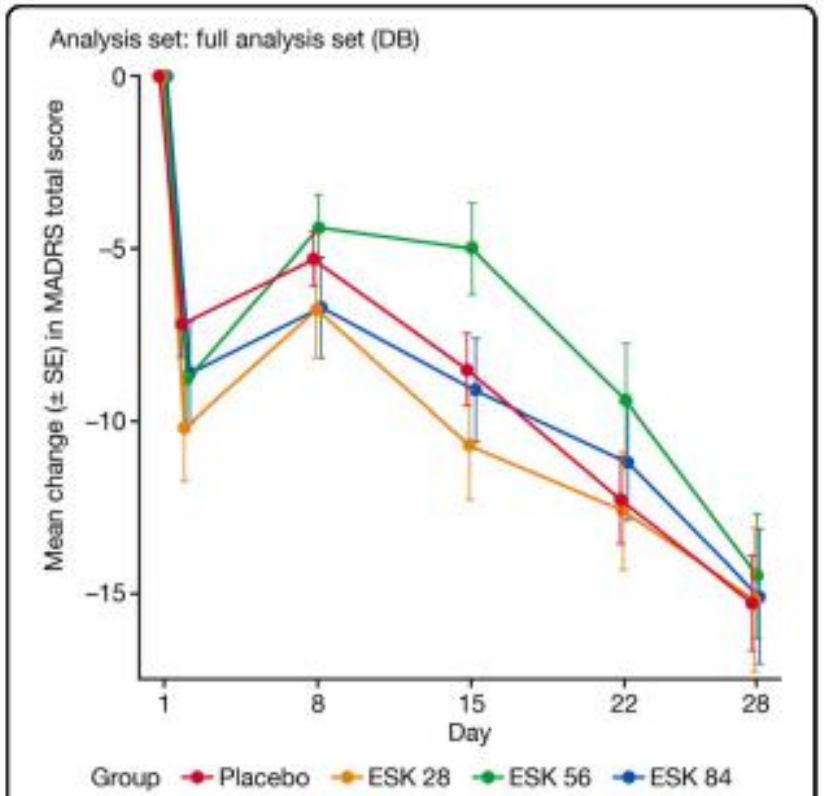


Fig. 2 Mean Change in MADRS Total Score Over Time Observed Case MMRM; DB Induction Phase. Abbreviations: DB = double-blind; Esk = esketamine; MADRS = Montgomery-Asberg Depression Rating Scale; MMRM = mixed-model for repeated measures; SE = standard error

Exemple de méthodologie

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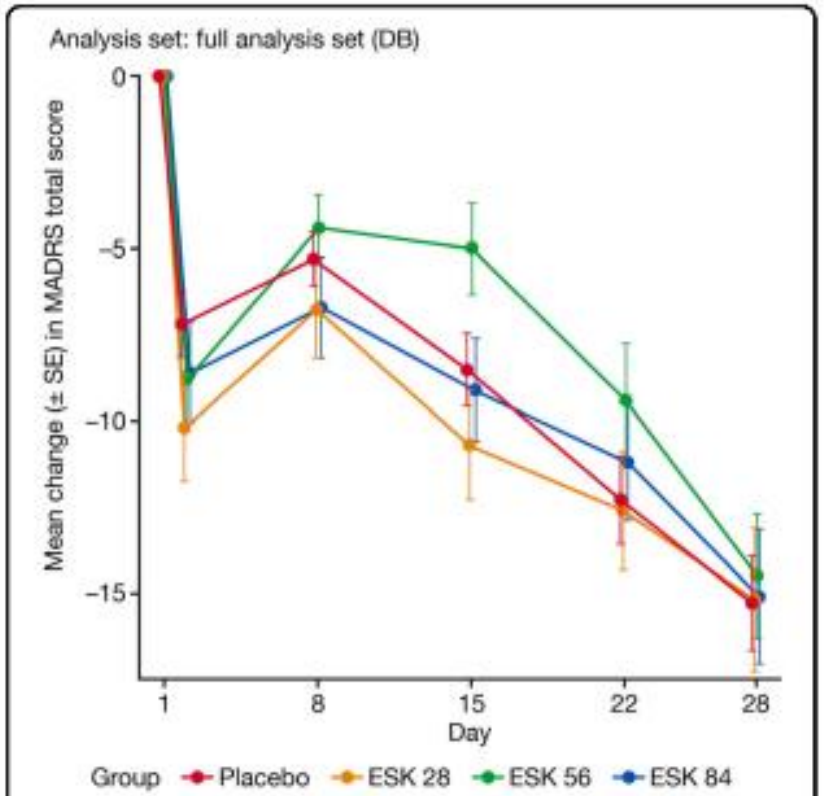

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Exemple de méthodologie

Table 4 TEAEs in At least 5% of Patients in any Treatment Group; DB Induction Phase

	Esk28 (*N* = 41)	Esk56 (*N* = 41)[a]	Esk84 (*N* = 40)	Comb Esk (*N* = 122)	Placebo (*N* = 80)
Patients with TEAEs, n (%)	**33 (80.5%)**	**39 (95.1%)**	**39 (97.5%)**	**111 (91.0%)**	**51 (63.8%)**
Blood pressure increased	12 (29.3%)	19 (46.3%)	19 (47.5%)	50 (41.0%)	8 (10.0%)
Dissociation	14 (34.1%)	10 (24.4%)	22 (55.0%)	46 (37.7%)	7 (8.8%)
Dizziness	11 (26.8%)	18 (43.9%)	15 (37.5%)	44 (36.1%)	5 (6.3%)
Somnolence	10 (24.4%)	13 (31.7%)	11 (27.5%)	34 (27.9%)	14 (17.5%)
Nausea	7 (17.1%)	7 (17.1%)	8 (20.0%)	22 (18.0%)	7 (8.8%)
Hypoaesthesia	7 (17.1%)	8 (19.5%)	5 (12.5%)	20 (16.4%)	4 (5.0%)
Vertigo	4 (9.8%)	7 (17.1%)	8 (20.0%)	19 (15.6%)	1 (1.3%)
Headache	6 (14.6%)	5 (12.2%)	4 (10.0%)	15 (12.3%)	3 (3.8%)
Asthenia	2 (4.9%)	7 (17.1%)	3 (7.5%)	12 (9.8%)	0
Sedation	1 (2.4%)	4 (9.8%)	5 (12.5%)	10 (8.2%)	0
Vomiting	1 (2.4%)	3 (7.3%)	4 (10.0%)	8 (6.6%)	3 (3.8%)
Feeling drunk	1 (2.4%)	5 (12.2%)	2 (5.0%)	8 (6.6%)	1 (1.3%)
Euphoric mood	0	4 (9.8%)	3 (7.5%)	7 (5.7%)	0
Hypoaesthesia oral	3 (7.3%)	2 (4.9%)	2 (5.0%)	7 (5.7%)	0
Diarrhoea	0	4 (9.8%)	2 (5.0%)	6 (4.9%)	3 (3.8%)
Malaise	0	3 (7.3%)	3 (7.5%)	6 (4.9%)	0
Dizziness postural	0	3 (7.3%)	2 (5.0%)	5 (4.1%)	0
Mental impairment	3 (7.3%)	2 (4.9%)	0	5 (4.1%)	0
Palpitations	1 (2.4%)	2 (4.9%)	2 (5.0%)	5 (4.1%)	1 (1.3%)
Diplopia	1 (2.4%)	3 (7.3%)	0	4 (3.3%)	0
Muscular weakness	0	2 (4.9%)	2 (5.0%)	4 (3.3%)	0
Dysarthria	1 (2.4%)	0	2 (5.0%)	3 (2.5%)	0
Hypotonia	0	0	3 (7.5%)	3 (2.5%)	0
Hallucination	0	1 (2.4%)	2 (5.0%)	3 (2.5%)	0
Suicidal ideation	0	1 (2.4%)	2 (5.0%)	3 (2.5%)	2 (2.5%)
Hyperacusis	0	1 (2.4%)	2 (5.0%)	3 (2.5%)	0
Oropharyngeal pain	0	1 (2.4%)	2 (5.0%)	3 (2.5%)	2 (2.5%)
Tinnitus	1 (2.4%)	0	2 (5.0%)	3 (2.5%)	0
Blood pressure diastolic increased	0	0	2 (5.0%)	2 (1.6%)	2 (2.5%)
Dyslalia	0	0	2 (5.0%)	2 (1.6%)	0
Respiratory rate decreased	0	0	2 (5.0%)	2 (1.6%)	0
Thirst	0	0	2 (5.0%)	2 (1.6%)	0
Weight increased	0	0	2 (5.0%)	2 (1.6%)	0

Exemple de méthodologie

Results: Of the 202 patients randomized in the DB induction phase (esketamine [*n* = 122] or placebo [*n* = 80]), the MADRS total scores decreased from baseline to Day 28 of the DB induction phase (– 15.2, – 14.5, – 15.1, and – 15.3 for esketamine 28 mg, 56 mg, 84 mg, and placebo groups, respectively), indicating an improvement in depressive symptoms; however, the difference between the esketamine and placebo groups was not statistically significant. The most common treatment-emergent adverse events during the DB induction phase in the combined esketamine group (incidences ranging from 12.3 to 41.0%) were blood pressure increased, dissociation, dizziness, somnolence, nausea, hypoaesthesia, vertigo, and headache; the incidence of each of these events was > 2-fold higher than the corresponding incidence in the placebo group.

Exemple de méthodologie

Vos conclusions ?

Exemple de méthodologie

Conclusions: Efficacy of esketamine plus oral AD in Japanese TRD patients was not established; further investigation is warranted. All esketamine doses were safe and tolerated.

Les études de phase IIb

Premiers **essais comparatifs** versus le traitement de référence et un placebo

Recherche de dose sur un petit nombre de dose (3 en moyenne) + placebo + traitement de référence

Différence avec un essai de phase III:

- Faible quantité d'information disponible avant le début de l'essai
- Nombre de patient plus faible
- Critères de jugement intermédiaires +++

Des questions ?