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#GPWInnovationDay online

Agenda

- CPL'280 - project status update
- Falkieri esketamine inhaler – update
- Q&As

Presenters

Maciej Wieczorek

PhD, CEO, Head of R&D

Paweł Buda

PhD, Preclinical Development Leader

Katarzyna Bazydło-Guzenda

Clinical Development Leader

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CPL'280 – project update

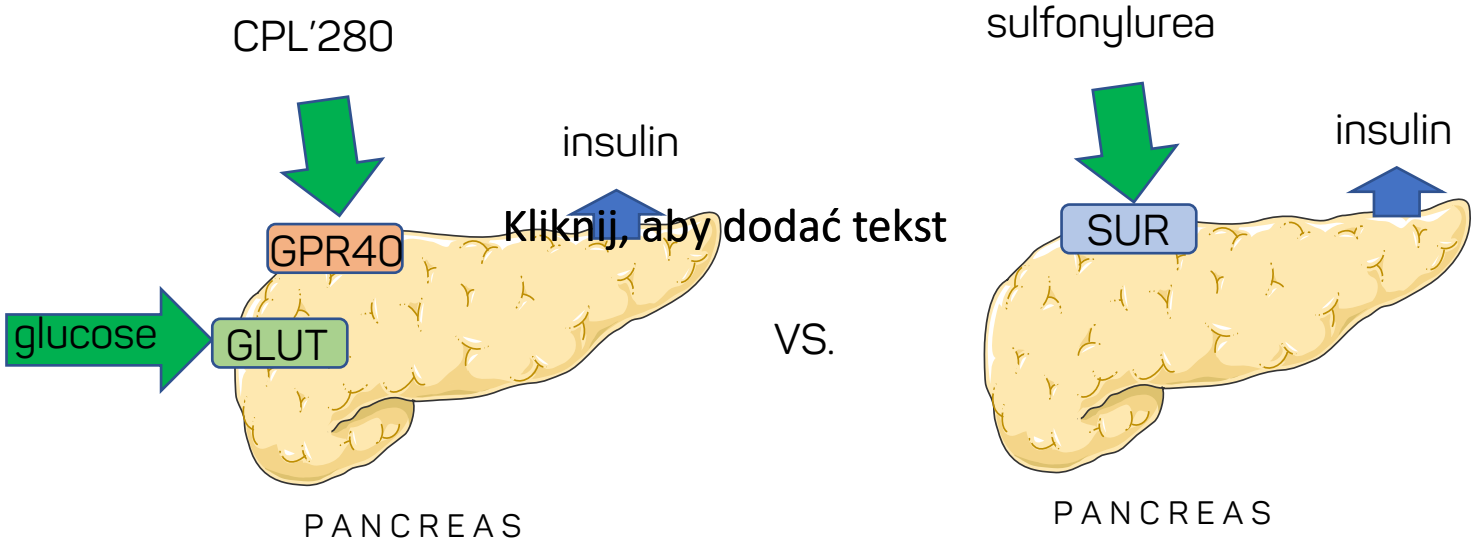
Second generation GPR40 agonist
for type 2 diabetes for oral administration

CPL'280 treatment: type 2 diabetes+diabetic neuropathy

Lower risk of hypoglycemia unlike the sulphonylureas

Clear safety profile no liver injury (hepatotoxicity) no significant bile acid transporter inhibition

There are 463 million people with diabetes globally with only 6% in good control - painful neuropathy is the most common complication



Kliknij, aby dodać tekst

GPR40 unique mechanism of action – glucose dependent release of insulin

Sulfonylurea - glucose independent release of insulin

sulfonylurea

Risk of hypoglycemia

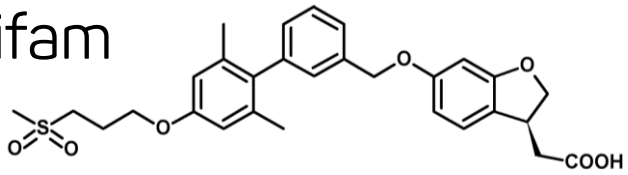
Induces weight gain

Contributes to progression of the disease – toxic to insulin-secreting cells

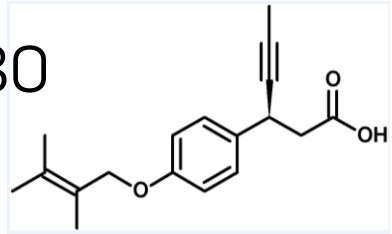
Secondary failures: unable to show sustainable effect

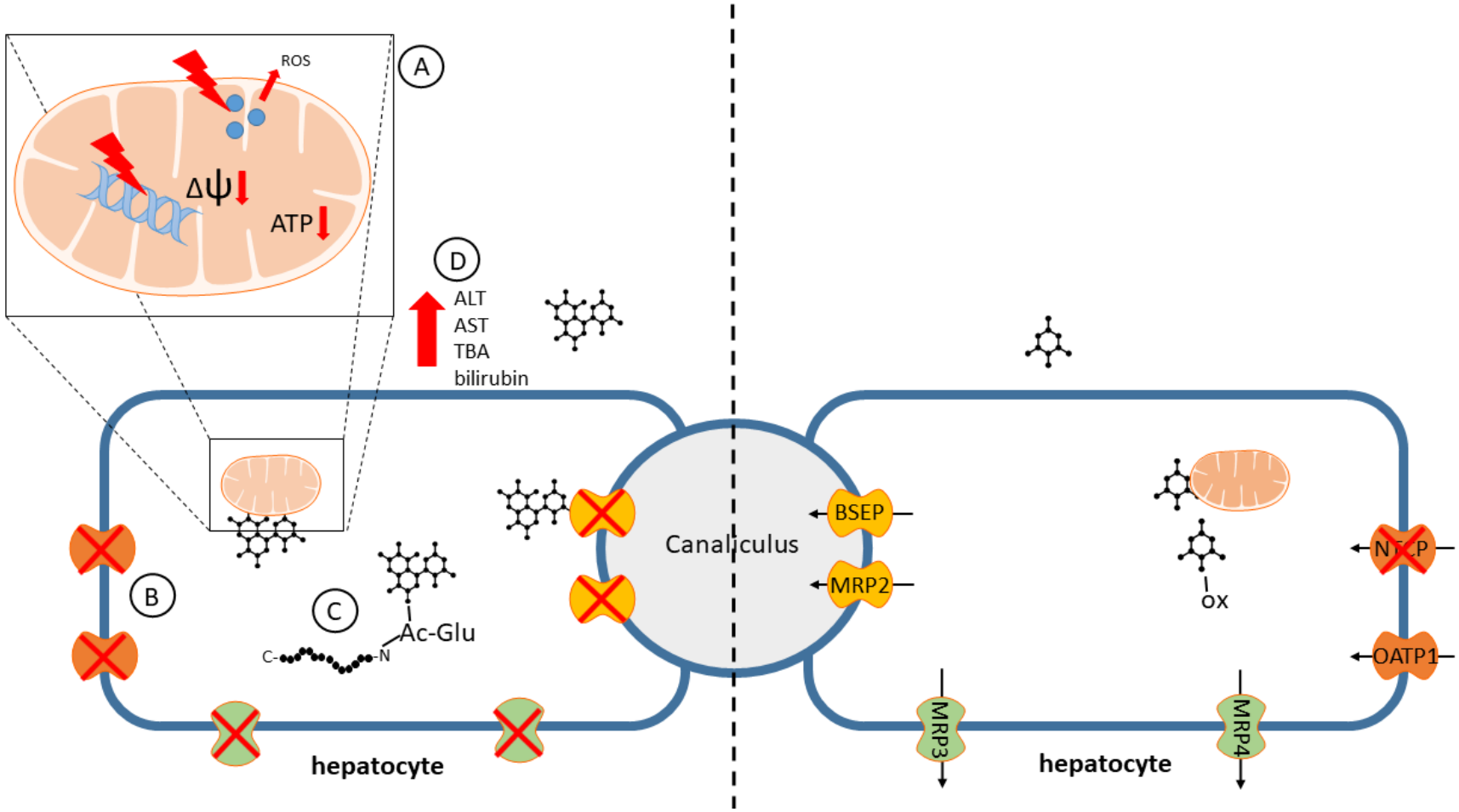
CPL'280 versus fasiglifam in liver toxicity

fasiglifam



CPL'280

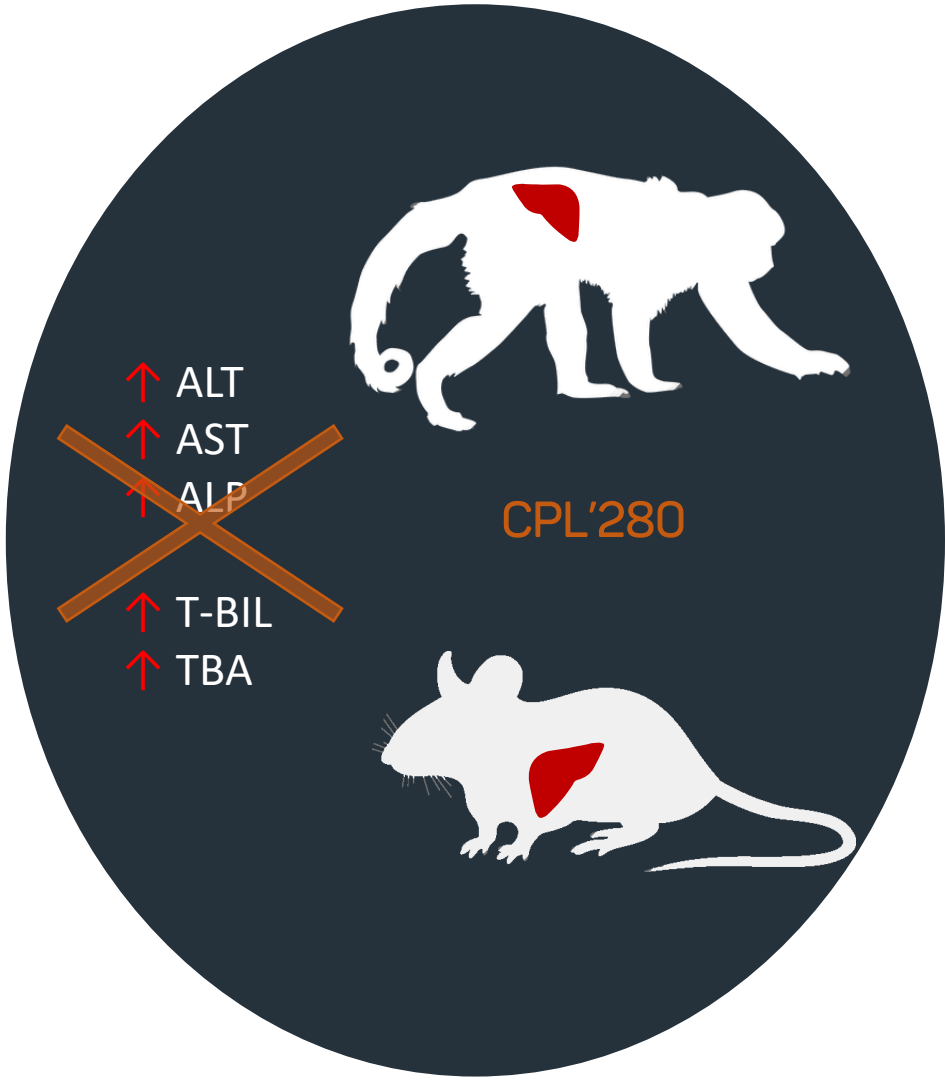




CPL'280 safety in animal models

In 56 days toxicology study CPL'280:

1. Was safe for the liver at doses 50x greater than the effective dose.
2. Did not alter safety liver markers: ALT, AST, ALP at doses, at which competitors showed overt liver toxicity.
3. Did not alter bile acids and bilirubin in plasma at doses, at which competitors significantly elevated them
4. Did not cause weight gain
5. Did not cause hypoglycemic events



CPL'280 efficacy in diabetic animal models

CPL'280 improved metabolic parameters:

1. Improved glucose tolerance
2. Reduced fasting glucose
3. Reduced metabolic syndrome (fats in serum and liver)
4. Improved function of insulin-secreting cells
5. Did not affect body mass
6. No hypoglycemic episodes.

ZDF rat

↑ glucose tolerance
↓ fasting glucose
↓ metabolic syndrome
↓ inflammation

ZDSD rat

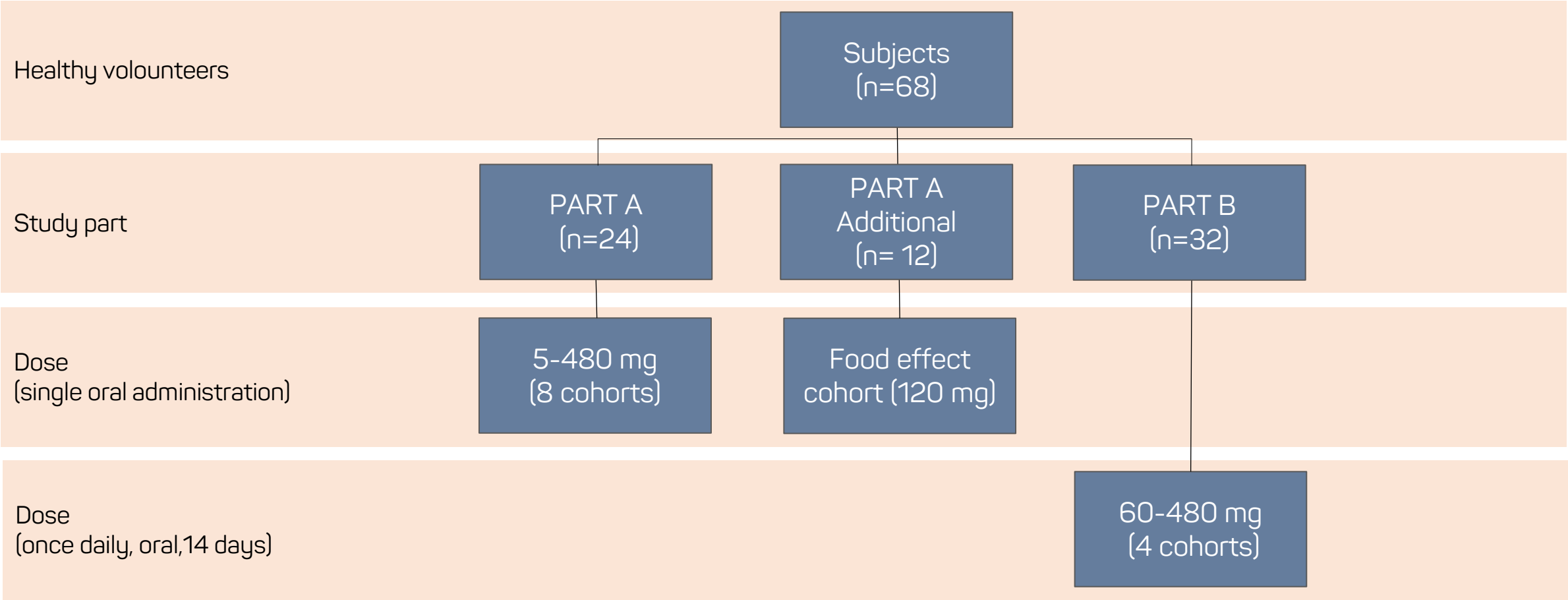
CPL'280

~~hypoglycemia~~
~~↑ body weight~~

db/db mice

Goto-Kakizaki (GK) rat

Phase 1 – "One Center, Single Ascending Dose and Double Blind Multiple Ascending Dose, Safety and Pharmacokinetics Phase I Study of CPL280 in Healthy Volunteers."

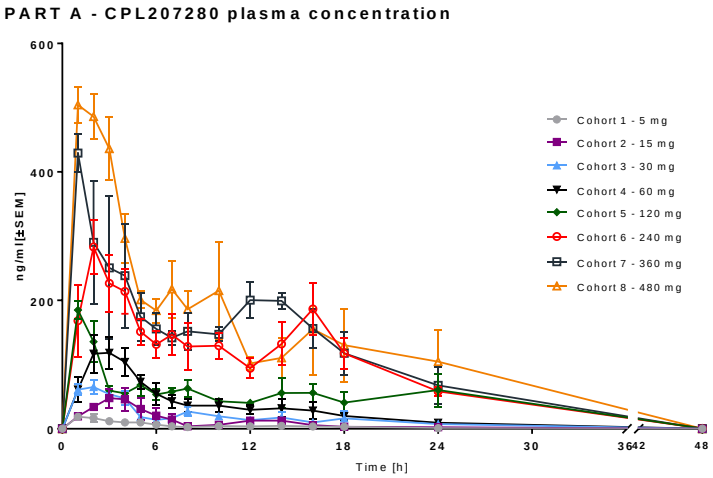


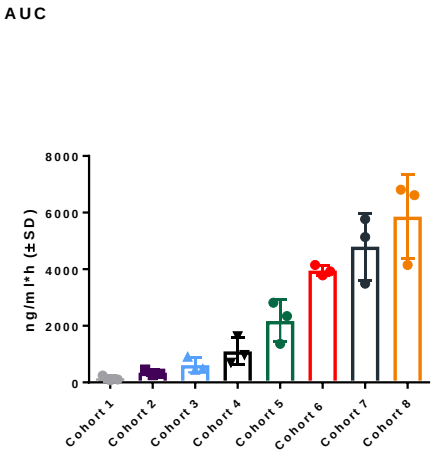
Primary objective:

To evaluate safety and tolerability after single and multiple (14 days) oral administration of CPL'280 in healthy volunteers.

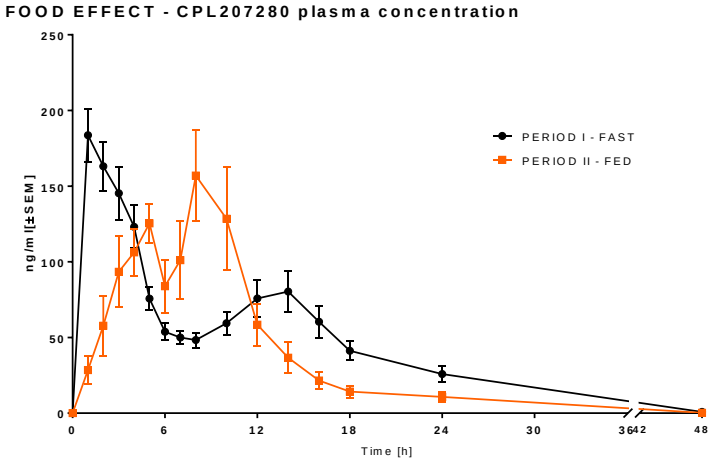
Phase 1 – Pharmacokinetic PART A – single oral administration

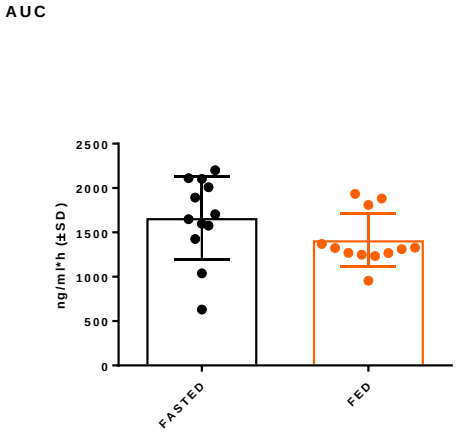
Pharmacokinetic profile of CPL'280 supports once daily administration





Food have no effect on the extent of CPL'280 bioavailability



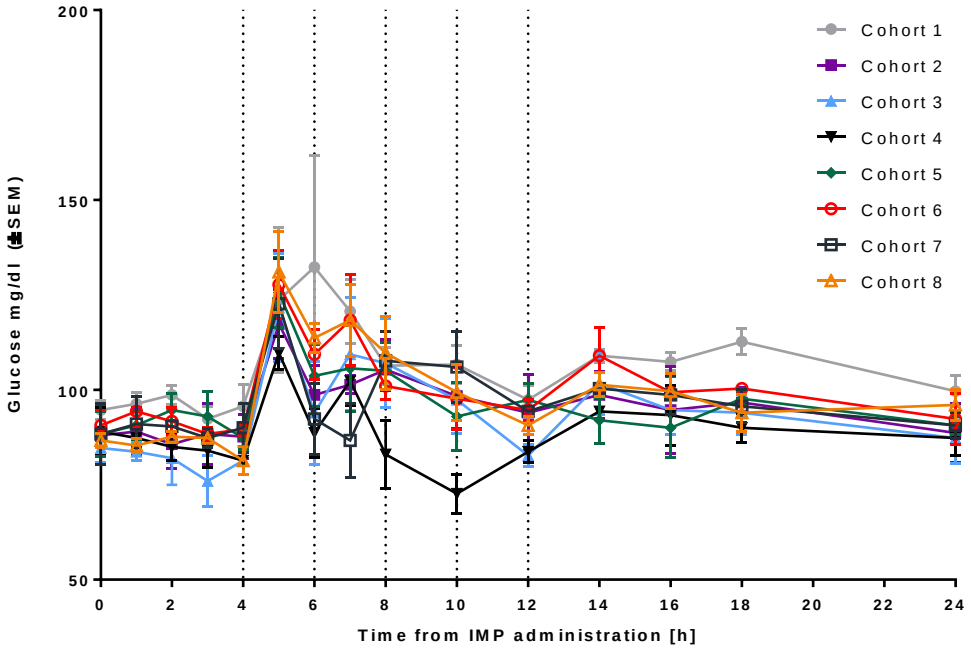


Phase 1 – Safety PART A – single oral administration

CPL'280 was generally safe and well tolerated with no serious adverse events (AEs)
All AEs classified as not related to the CPL'280, most AEs classified as mild and few classified as moderate.

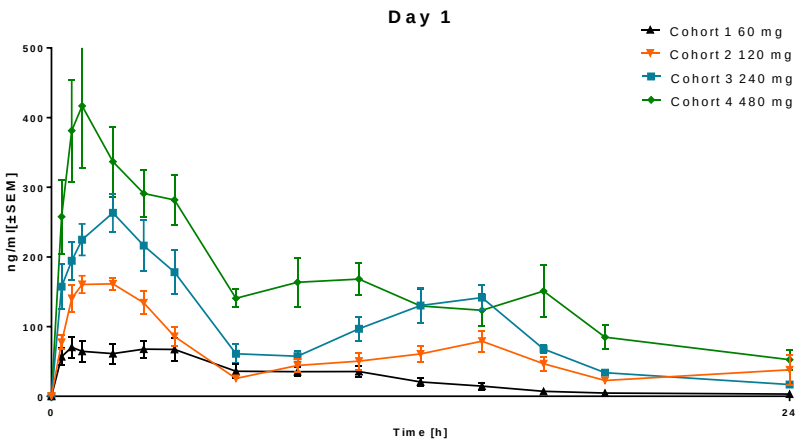
No hypoglycemia episodes were reported during the PART A of the study

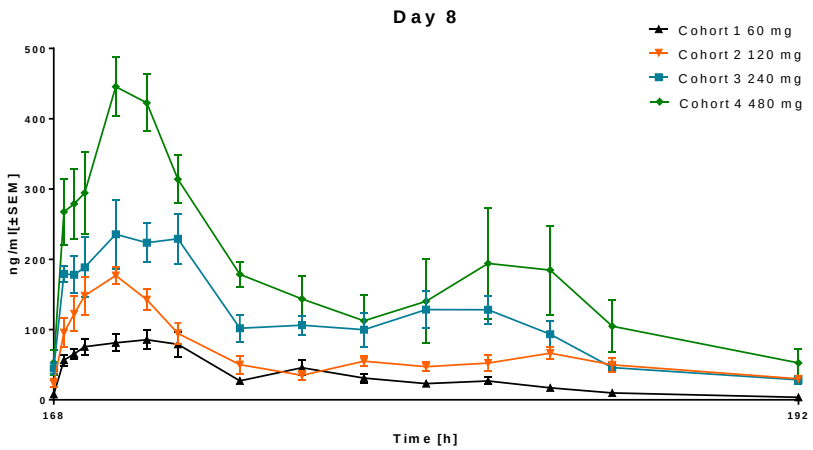
PART A AE description	AE observed (N(%))	Subjects affected (N(%))
headache	3 (21.4%)	3 (12.5%)
elevated ALT level	2 (14.3%)	2 (8.3%)
leucocyturia	2 (14.3%)	2 (8.3%)
elevated AST level	1 (4.2%)	1 (7.1%)
increased creatine kinase (CK)	1 (4.2%)	1 (7.1%)
urinary track candidiasis suspicion	1 (4.2%)	1 (7.1%)
runny nose	1 (4.2%)	1 (7.1%)
soft faeces	1 (4.2%)	1 (7.1%)
ischias	1 (4.2%)	1 (7.1%)
elevated blood glucose level	1 (4.2%)	1 (7.1%)
Total	**14 (100.0%)**	**24 (100.0%)**

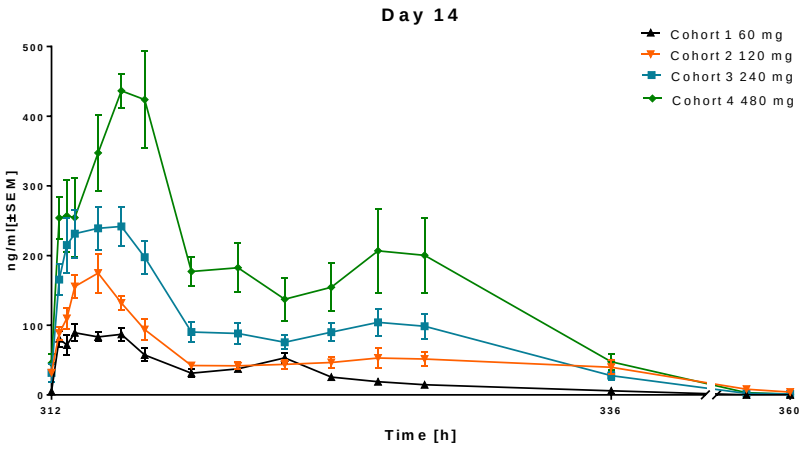


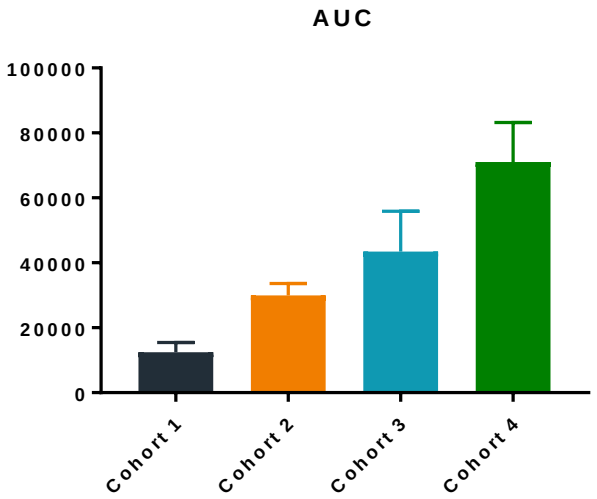
*Black vertical lines denote time of meals.

Phase 1 – Pharmacokinetic PART B – 14 days oral administration









Phase 1 – Safety PART B – 14 days oral administration

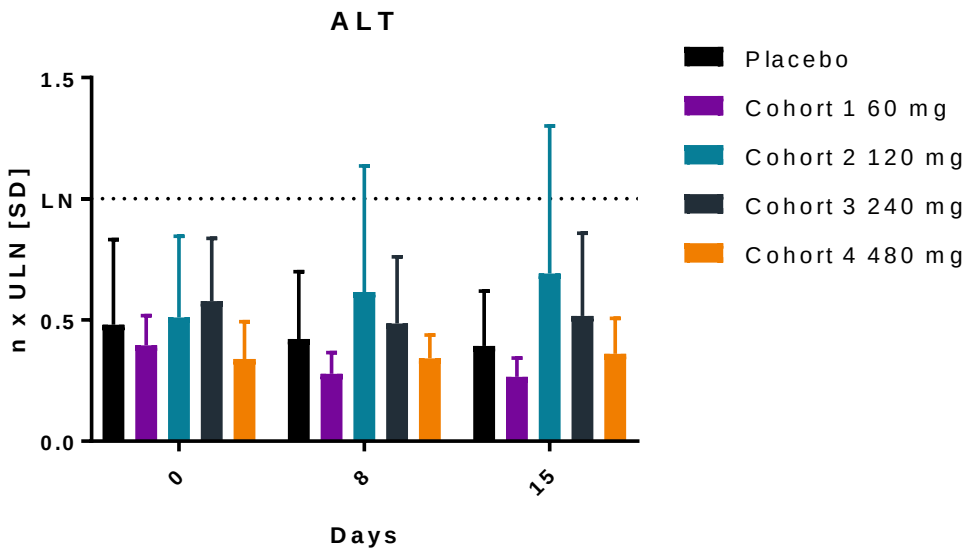
CPL'280 was generally safe and well tolerated with no serious adverse events (AEs)
All AEs classified as not related to the CPL'280, most AEs classified as mild and few classified as moderate.

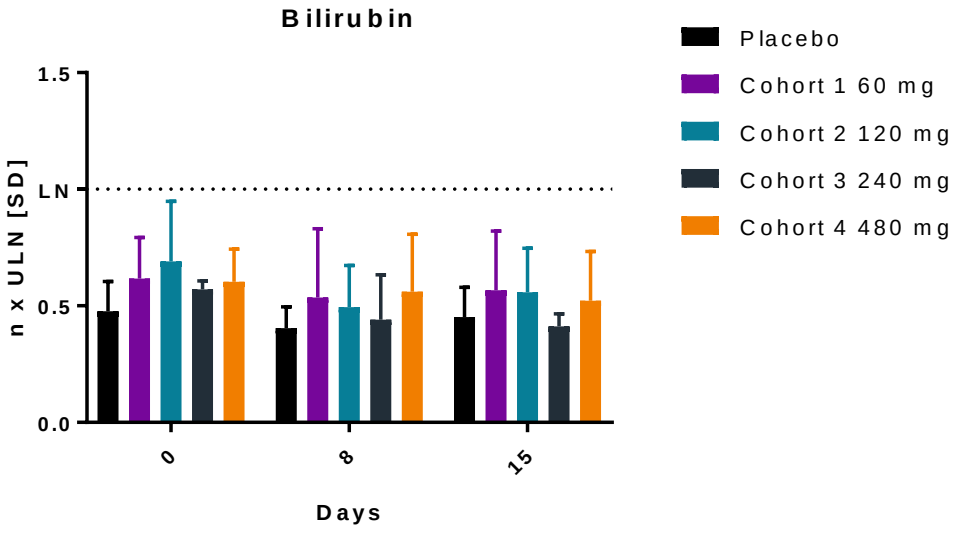
No hypoglycemia episodes were reported in PART **B** of the study

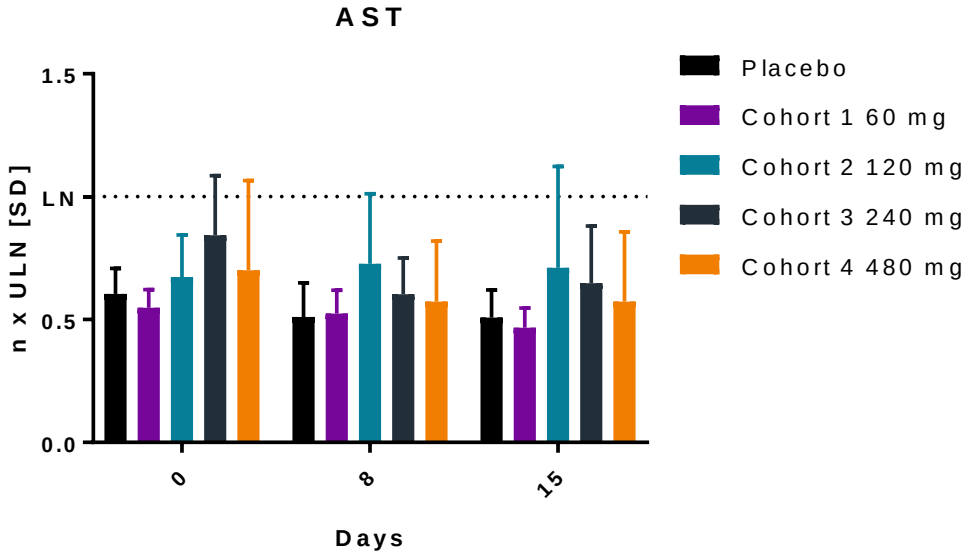
PART A AE description	AE observed N(%)	Subjects affected N(%)
headeche	8 (33%) (4 placebo)	5 (16%)
elevated level of alt (alanine transaminase)	3 (20%)	3 (9%)
increased creatine kinase (CK)	2 (13%)	2 (6%)
constipation	2 (13%)	2 (6%)
elevated level of ast (aspartate transaminase)	2 (13%)	2 (6%)
abdominal pain	2 (13%)	2 (6%)
elevated bilirubin level	1 (4%)	1 (3%)
pain in the spine	1 (4%)	1 (3%)
elevated bile acids	1 (4%) (placebo)	1 (3%)
transient cardiac arrhythmia (AV block II degree)	1 (4%)	1 (3%)
foodborne illness	1 (4%)	1 (3%)
Total	24	32

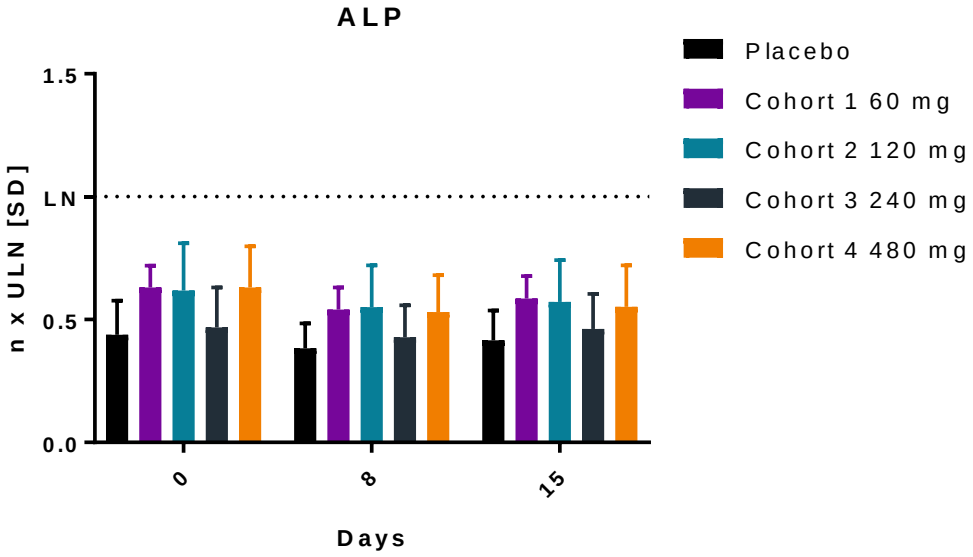
	Total	N	24
PART B	Dose	60 mg	4
		120 mg	7
		240 mg	3
		480 mg	5
		Placebo	5
	Intensity	Mild	9
		Moderate	15
		Severe	0
	Relationship to IMP	Not related	24
		Possible related	0
		Related	0

Phase 1 – Safety PART B

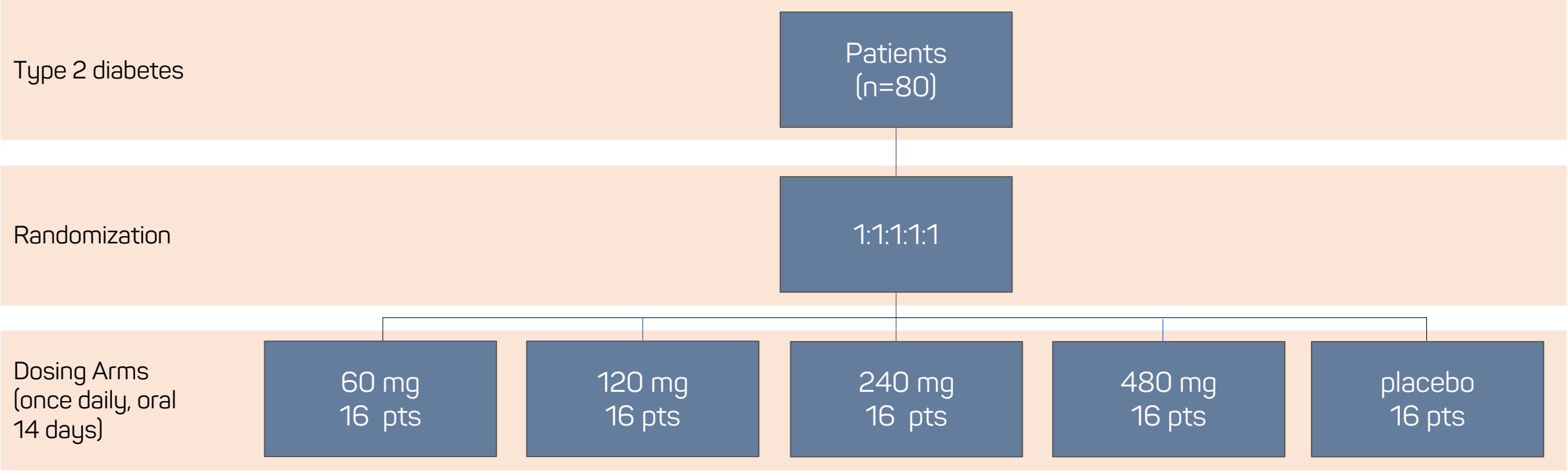








Phase 2 – Efficacy, Safety and Pharmacokinetics after 2-weeks in Subjects With Type 2 Diabetes



Primary objective:

To determine the efficacy in lowering plasma glucose - OGTT (oral glucose tolerance test) after 2 weeks of CPL'280 treatment.

CPL'280 - GPR40 agonist for oral administration

Designed to Improve on Sulfonylureas Limitations

Diabetes Type 2 – Where We Are Aiming

- Metformin is the first line oral treatment, new agents (GLP1, SGLT2) show slow uptake in first-line
- Sulfonylureas still used by 20-40% of patients in second or third line where there is inadequate response to first/second line agents[1]
- Good efficacy and cost-effectiveness profiles are major reasons behind use of sulfonylureas[1]
- Hypoglycemia risk, weight gain and lack of evidence of "benefit beyond glucose control" are major limitations for wider sulfonylurea use[1]

GPR40 might Substitute Sulfonylureas

- CPL'280 is unlikely to be associated with hypoglycemia risk or weight gain
- Fasiglifam showed neutral impact on weight and no hypoglycemia risk, significantly lower than glimepiride[2,5]
- Fasiglifam announced interim Phase 3 outcome CV study, which showed no evidence of increased CV risk (HR 1.05; 95% CI 0.67, 1.63)[3]

CPL'280 Targets $7 Bn Market of Sulfonylureas

- 420 m people with type 2 diabetes globally with only 6% in good control - painful neuropathy is the most common complication
- Pharmaceutical market size is estimated to be $50 bn + with CAGR >7%[4]
- Ca. 75-100 m patients treated with sulfonyruleas at the average monthly cost of $10 or less
- The sulfonylureas market is saturated with moderate CAGR of 2.7% expected in the next years and value of $7 bn in 2023[1]
- North America accounts for close to 44% of the global market share of sulfonylureas followed by China (17.5%)[1]
- **CPL'280 could substitute sulfonylureas if better safety profile is confirmed in further clinical development**
- **Potential diabetic neuropathy claim would provide clear differentiation**

Sales data, market valuations from EvaluatePharma, 2021

1. Mordor Intelligence 2019, Sulfonylureas Market – Segmented by Drugs, and Geography – Growth, Trends, and Forecast (2020 - 2025) (mordorintelligence.com)
2. Marcinak J et al., Diabetes Obes Metabol, 2017 Dec;19(12):1714-1721
3. Menon V et al., Diabetes Care 2018;41:2603–2609
4. Research and Markets 2018, https://www.researchandmarkets.com/reports/3821046/global-diabetes-market-research-and-forecast
5. Burant et al., Lancet 2012 Apr 14;379(9824):1403-11

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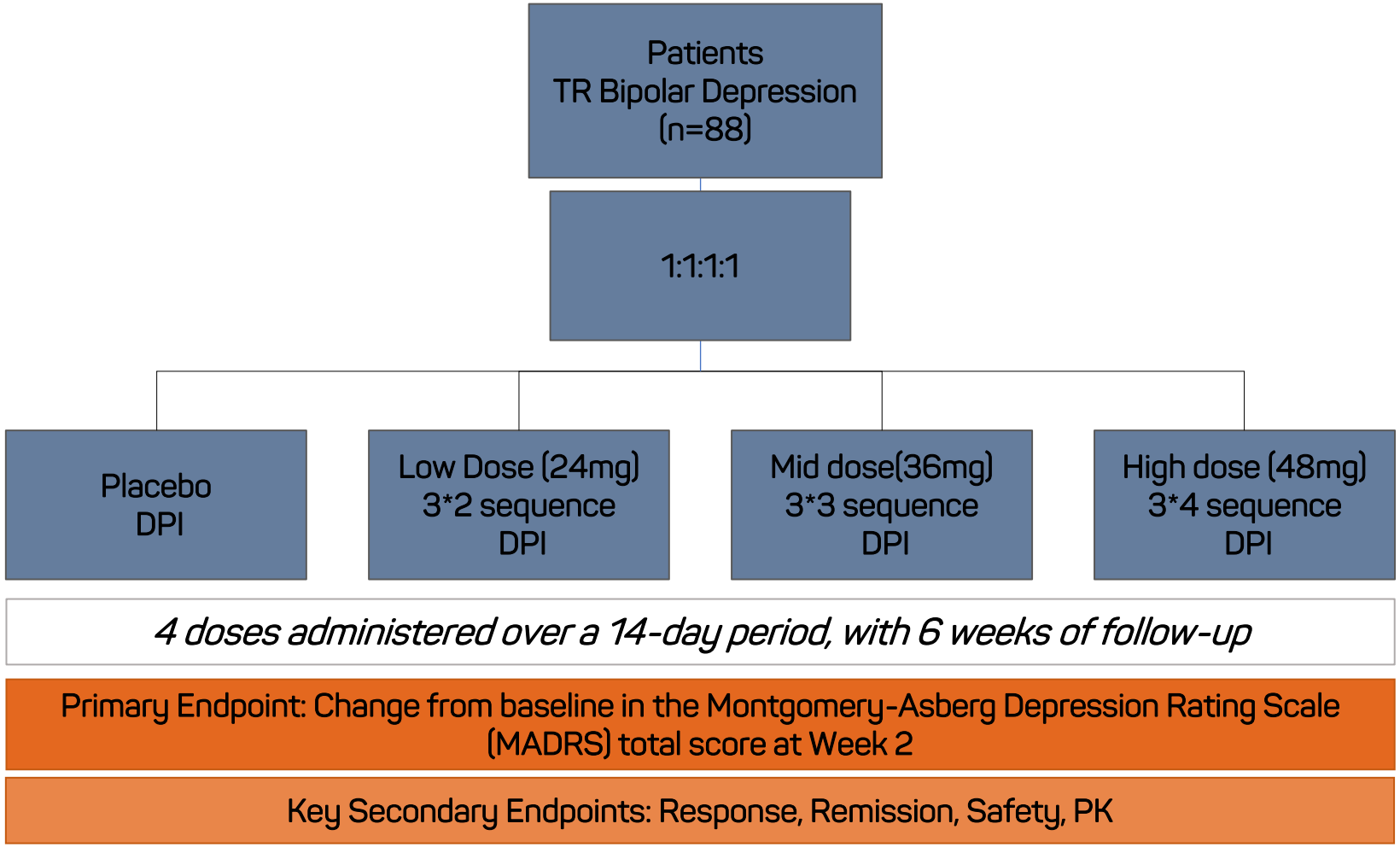
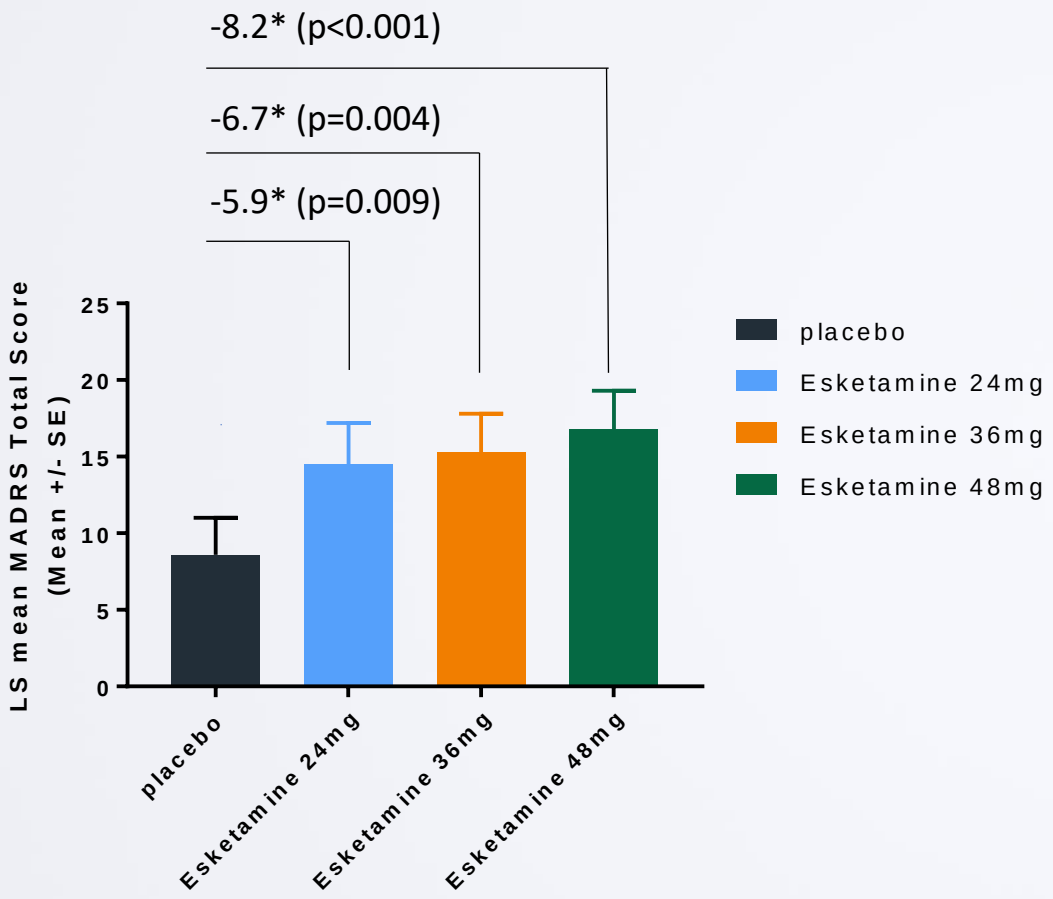
03KET2018 – Phase 2 TRBD update

Falkieri Phase II TR Bipolar Depression Trial - Design Summary



NCT03965871: randomized, double blind, placebo controlled, multicentre study using Falkieri as an adjunctive treatment.

Falkieri Primary Efficacy Endpoint Successfully Met (Change in MADRS Total Score at Week 2)



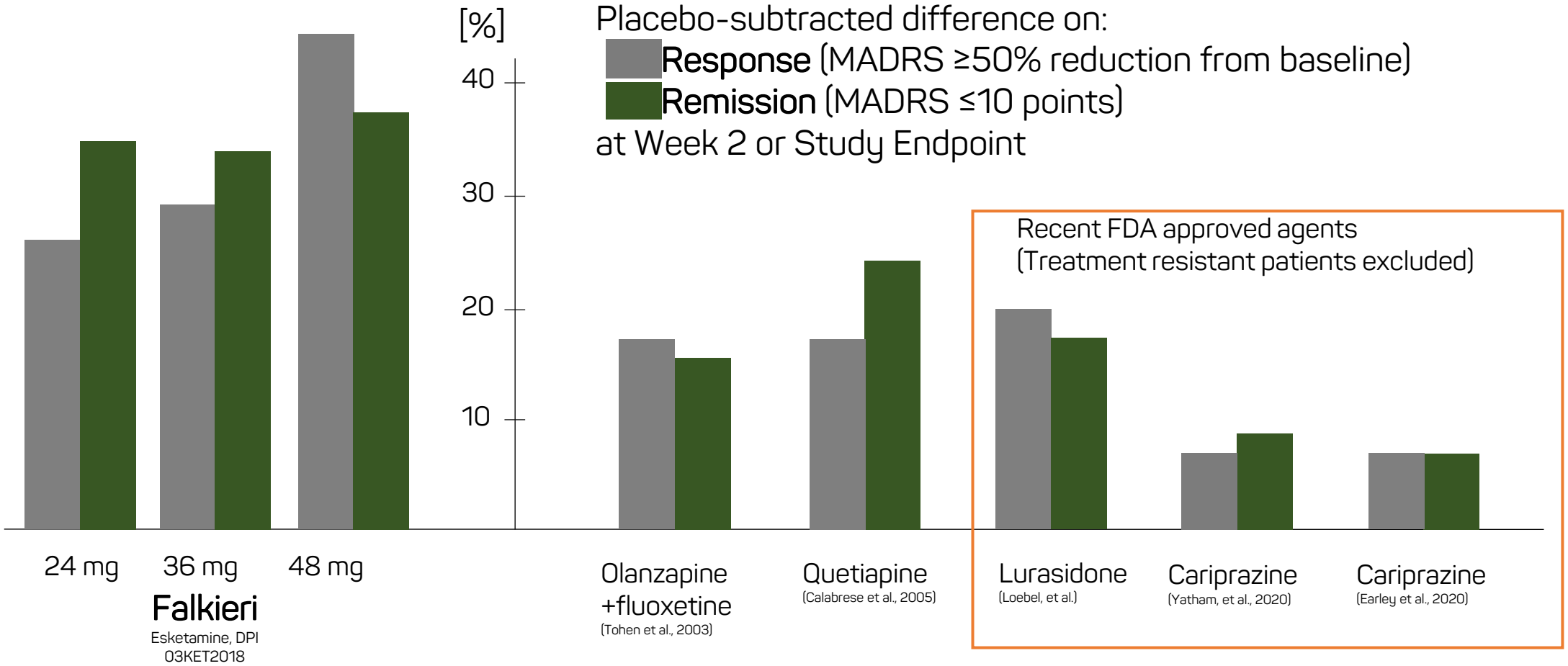
	Placebo (N=22)	Esketamine		
		24 mg (N=23)	36 mg (N=21)	48 mg (N=22)
Mean ChfB (SD)	-7.0 (6.7)	-13.7 (8.3)	-14.6 (8.1)	-16.5 (6.4)
LS mean ChfB (SE)	-8.6 (2.4)	-14.5 (2.7)	-15.3 (2.5)	-16.8 (2.5)
LS mean difference vs placebo (SE)		**-5.9 (2.2)**	**-6.7 (2.2)**	**-8.2 (2.2)**
95% CI for LS mean difference vs placebo		-10.2 - -1.5	-11.1 - -2.2	-12.6 - -3.7
p-value vs placebo		0.009	0.004	< 0.001
Effect size (Cohens D)		0.888	1.017	1.434

ChfB: change from baseline
CI: confidence interval

Falkieri demonstrated a rapid and substantial improvement in the symptoms of depression in all tested doses.

p-value calculate from LS means. Placebo-subtracted diffirences. Based on ANCOVA analysis
Celon Pharma. Data on File 2021

Falkieri Efficacy Data in Achieving **RESPONSE and REMISSION** Compares Favorably to Other Therapeutic Options



Falkieri efficacy data compare favorably to other agents.
Both response and remission rates for Falkieri exceed those for other agents.

The data for other treatments measured at timepoint between Week 2 and 8 depending on the data availability.
Celon Pharma. Data on File 2021

Falkieri Safety Profile in Bipolar Depression

- No deaths, no serious side effects, no suicides, no discontinuations due to adverse events, no mania induction at any time point, no sedation
- No dose related adverse events (% of subjects with adverse events: Placebo – 27.3%, Esk24 – 39.1%, Esk36 – 23.8%, Esk48 – 27.3%),

Adverse events occurring in ≥ 5% of patients

No.	Adverse Events	Overall (N=88)	Placebo (N=22)	Esketamine		
				24 mg (N=23)	36 mg (N=21)	48 mg (N=22)
1	Dizziness	18 (20.5%)	2 (9.1%)	9 (39.1%)	3 (14.3%)	4 (18.2%)
2	Feeling abnormal	13 (14.8%)	2 (9.1%)	6 (26.1%)	3 (14.3%)	2 (9.1%)
3	Euphoric mood	7 (8.0%)	0 (0.0%)	4 (17.4%)	2 (9.5%)	1 (4.5%)

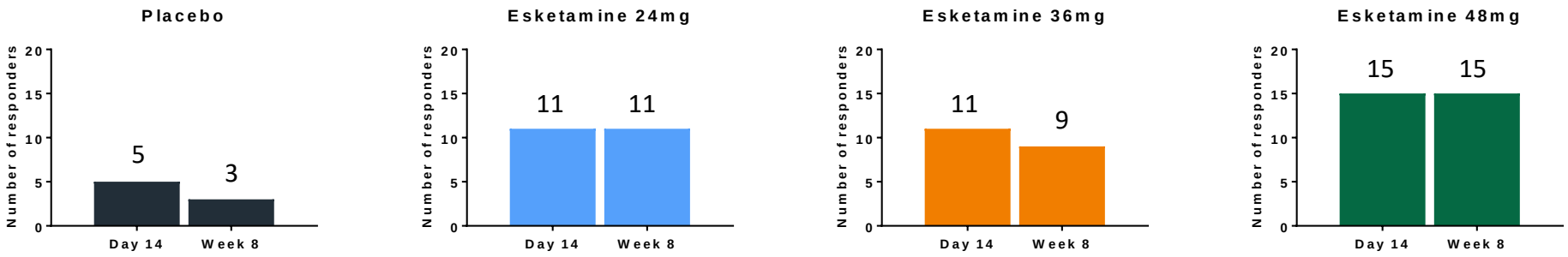
[N, (% of patients)]

Clean safety profile. High study completion rates.

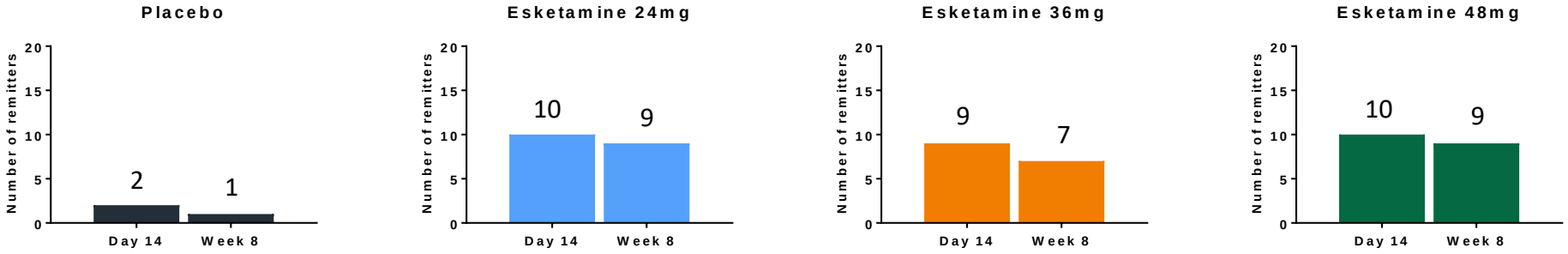
Celon Pharma. Data on File 2019

Response and remission observed at the end of 6 - week observation phase

Clinical response (defined as ≥50% MADRS total score reduction from baseline)



Clinical remission (defined as MADRS total score ≤10)



Observation of clinical response and remission at Week 8 assessed only for responders (patient having clinical response on Day 14) and remitters (patient having clinical remission on Day 14), respectively.

No deaths, no serious side effects, no suicides were reported. General safety profile consistent with previous study.

* Based on data available on 23rd June 2021

2021/2022 Clinical Trials News Flow

2Q 2021

FALKIERI treatment resistant bipolar depression – final Phase 2 results

CPL'280 (GPR40) – multiple administrations – Phase 2 in diabetes starts

FALKIERI – Phase 3 regulatory feedback applications

3Q 2021

CPL'116 (JAK/ROCK) – final Phase 1 results

CPL'116 (JAK/ROCK) – Phase 2 in selected autoimmunology diseases (RA, Ps, IPF) starts

CPL'116 (JAK/ROCK) – Phase 2/3 in hospitalized COVID patients starts

FALKIERI – Phase 3 regulatory feedback

4Q 2021

CPL'280 (GPR40) – first stage of Phase 2 results in type 2 diabetes

CPL'110 (FGFR) – Phase 1/1b results in solid tumors

FALKIERI – Phase 3 starts

1Q/2Q 2022

CPL'110 (FGFR) – Phase 2/2 b (of key importance) in 2 selected tumours starts

CPL '36 (PDE10a) – key Phase 2 POCs readouts (schizophrenia and PD)

CPL'116 (JAK/ROCK) – results of Phase 2 PoC in selected AI diseases

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Dziękujemy za uwagę