A PHASE I TRIAL OF THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF CANNABIDIOL ADMINISTERED AS SINGLE-DOSE OIL SOLUTION AND SINGLE AND MULTIPLE DOSES OF A SUBLINGUAL WAFER IN HEALTHY VOLUNTEERS

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Published in *British Journal of Clinical Pharmacology*. 2020 Oct 19. DOI: 10.1111/bcp

OBJECTIVES

To determine the safety, tolerability, and pharmacokinetics (PK) of a specific *Cannabis sativa* cultivar extract standardised to CBD content (LINNEA 315CSE™ extract- MediCabilis™) when administered as an oil formulation or sublingual wafer, and compared to nabiximols oromucosal spray.

BACKGROUND

Cannabidiol (CBD) is a non-intoxicating constituent of the cannabis plant that has shown therapeutic efficacy for multiple conditions; such as epilepsy and anxiety.

Furthermore each *Cannabis sativa* cultivar has a unique combination of cannabinoids which provides it's therapeutic characteristics.

There is limited information on the pharmacokinetic (PK) activity of CBD and specific *Cannabis sativa* cultivars in humans.

SUMMARY OF FINDINGS

- LINNEA 315CSE™ extract was safe and well tolerated when administered as a single dose of CBD 50 mg (1 mL of MediCabilis™).
- LINNEA 315CSE™ extract's safety profile was consistent with CBD safety data described in the literature.
- PK data for the LINNEA 315CSE™ extract as an oil showed that CBD was detectable in the plasma shortly after administration, reached peak plasma concentrations 4 h post-administration and remained detectable for 12 -24 hours.
- The confirmation of low THC content for the *Cannabis sativa* LINNEA 315CSE™ extract was reassuring in term of avoiding unwanted potential intoxicating effects of THC.

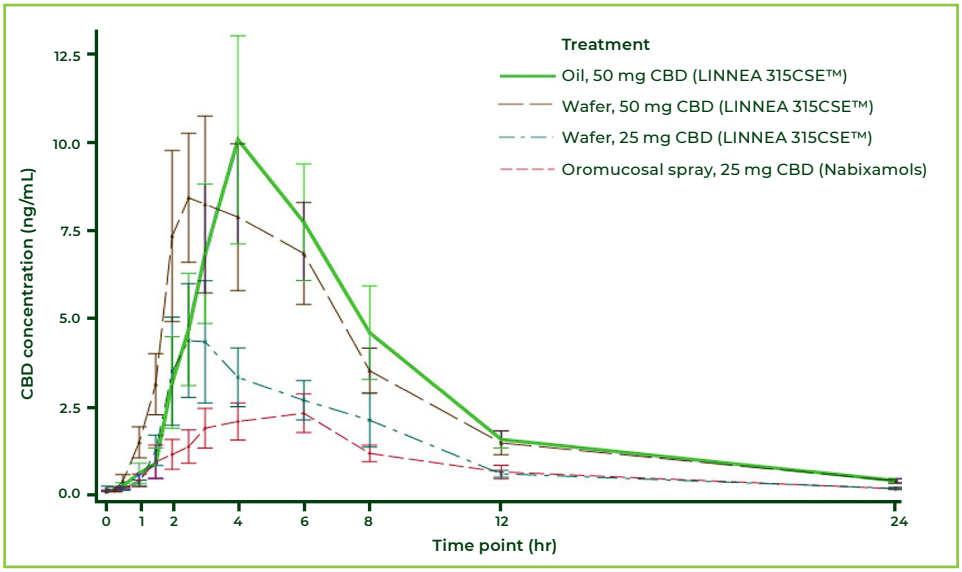
KEY SAFETY RESULTS:

- There were no serious adverse events reported.
- The most common related adverse events were somnolence, sedation and altered mood. Adverse events were all mild or moderate in severity.
- No clinically significant abnormalities were reported in vital signs, ECG, physical findings or safety laboratory tests.
- There were less adverse events reported for the LINNEA 315SCE™ extract than the nabixamols spray.

PHARMACOKINETICS RESULTS

- The plasma exposure of CBD increased in a dose-proportional manner.
- CBD plasma concentrations increased rapidly after administration, with maximum plasma levels measured at 4 h and CBD remaining detectable in plasma for 12-24 h.
- LINNEA 315CSE™ extract was found to provide bioavailable CBD, achieving a high concentration of CBD when administered in the form of an oil solution or wafer.
- The absence of detectable plasma THC concentrations after administering the LINNEA 315CSE™ extract as a single dose of wafer (25 mg CBD and 50 mg CBD) or oil solution (50 mg CBD) confirmed the low THC content of the extract.

Mean plasma CBD concentration – time profiles



Mean plasma CBD concentration-time profiles after a single dose of LINNEA 315CSE™ extract for the 3 dose forms and the Sativex (nabiximols) oromucosal spray in 12 healthy participants; the error bars represent ±SD. Values for nabiximols 20 mg CBD were normalised to 25 mg CBD.

CBD pharmacokinetic parameter by treatment for single dose study in 12 healthy participants

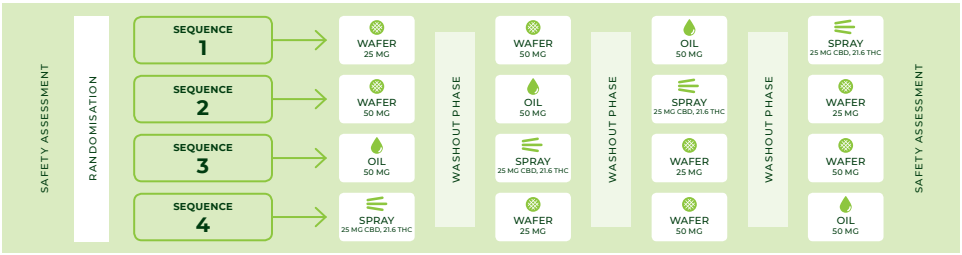
	Oil 50 mg CBD	Wafer 50 mg CBD	Wafer 25 mg CBD	Oromucosal spray 20 mg CBD[a]
Parameter	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ng mL^{-1})	**14.0 ± 9.3**	15.0 ± 8.9	9.1 ± 6.7	4.6 ± 2.4
T_{max} (h)	**5.2 ± 1.8**	4.1 ± 2.0	4.5 ± 2.2	4.5 ± 2.0
AUC_{0-t} (ng h mL^{-1})	**69.8 ± 34.1**	67.3 ± 29.5	31.1 ± 12.9	26.6 ± 11.2
$AUC_{0-\infty}$ (ng h mL^{-1})	**73.8 ± 35.2**	71.0 ± 1.8	33.5 ± 13.9	29.3 ± 12.3
Apparent clearance (CL/F)[b] (L h^{-1})	**826 ± 366**	740 ± 397	872 ± 356	810 ± 317

a Values for nabiximols 20 mg CBD were normalised to 25 mg CBD b After oral dosing CL/F = Dose/ $AUC0-_{0-\infty}$

METHODS

Single-dose study:

- Open label, four-way crossover in 12 healthy volunteers.
- Randomised to receive one of four treatment sequences with a washout period of 24 h between dosing.



- For each treatment sequence, the following assessments were performed:
  - **Safety Assessments:** Vital signs, 12-Lead ECG, laboratory evaluation pre-dose and 1, 3, 6, 12 and 24 h post-dose.
  - **Pharmacokinetics Blood Samples:** Serial blood samples were taken at pre-dose, then 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 12 and 24 h post-dose.

PARTICIPANT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristics	Single Dose Study N = 12 (Range)
Age (Yrs.)	33 (32–49)
Height (cm)	179 (162–200)
BMI (kg m-2)	25 (20–29)
Weight (kg)	81 (66–108)
Sex	1 Female, 11 Male
Geographic ancestry	2 Asian, 10 Caucasian

TREATMENT-EMERGENT ADVERSE EVENTS IN SINGLE DOSE STUDIES

	Number of subjects reporting an adverse event. n (%)			
System Organ Class / Preferred Term	CBD Oil 50 mg CBD	Wafer 50 mg CBD	Wafer 25 mg CBD	Oromucosal spray (20 mg CBD)
	n=12	n=12	n=12	n=12
Any adverse event	4 (33)	5 (42)	2 (17)	10 (83)
Eye disorders	-	-	-	2 (17)
Eye irritation	-	-	-	2 (17)
Gastrointestinal disorders	1 (8)	1 (8)	-	1 (8)
Abdominal pain	-	1 (8)	-	-
Nausea	1 (8)	-	-	1 (8)
General disorders and administration site conditions	-	-	-	2 (17)
Fatigue	-	-	-	1 (8)
Feeling drunk	-	-	-	1 (8)
Infections and infestations	-	1 (8)	-	1 (8)
Upper respiratory tract infection	-	1 (8)	-	1 (8)
Injury, poisoning and procedural complications	1 (8)	-	-	-
Contusion	1 (8)	-	-	-
Nervous system disorders	3 (25)	3 (25)	2 (17)	5 (42)
Dizziness	-	-	-	1 (8)
Presyncope	1 (8)	-	-	-
Sedation	1 (8)	1 (8)	-	2 (17)
Sensory disturbance	1 (8)	-	-	1 (8)
Somnolence	1 (8)	2 (17)	2 (17)	2 (17)
Psychiatric disorders	-	1 (8)	-	5 (42)
Agitation	-	-	-	1 (8)
Anxiety	-	-	-	1 (8)
Disorientation	-	-	-	1 (8)
Dysphoria	-	-	-	1 (8)
Euphoric mood	-	-	-	2 (17)
Mood altered	-	1 (8)	-	-

For full details of the study and results,
click here for the article or scan the QR code.
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