CANCER APPETITE RECOVERY STUDY (CARES): STUDY PROTOCOL FOR A DOSE-ASCENDING, MULTICENTER, RANDOMIZED CONTROLLED PHASE 1/2 TRIAL OF ART27.13 IN PATIENTS WITH CANCER ANOREXIA AND WEIGHT LOSS

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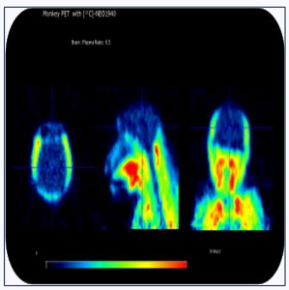
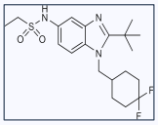
BACKGROUND

The cannabinoid 1 (CB_1) receptor regulates appetite and body weight, however, unwanted central side effects of both agonists (in wasting disorders) and antagonists (in obesity and diabetes) have limited their therapeutic utility. The next generation of these potential medicines have been peripherally restricted to mitigate these issues. ART27.13 (Artelo Biosciences) is a development stage CB_1/CB_2 receptor agonist with reduced brain penetration. As shown below it is structurally diverse from THC and acts as a full agonist compared to THC being a partial agonist. In otherwise healthy subjects who participated in a Phase 1 pain study it was observed that low doses of ART27.13 rapidly increased body weight of more than 3% that was not explained by fluid retention and without serious or persistent side effects. Anorexia affects over 60% of late-stage cancer patients for which there is no pharmacologic intervention recognised as the standard of care. ART27.13 may prove to increase appetite, lean body mass, and weight in people with cancer anorexia cachexia syndrome (CACS).

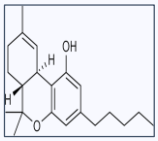
ART27.13 – CB_1 and CB_2 dual Agonist that was designed to be peripherally selective[2]



Monkey PET Scan with [^{11}C]-ART27.13
Brain: Plasma Ratio = 0.5.



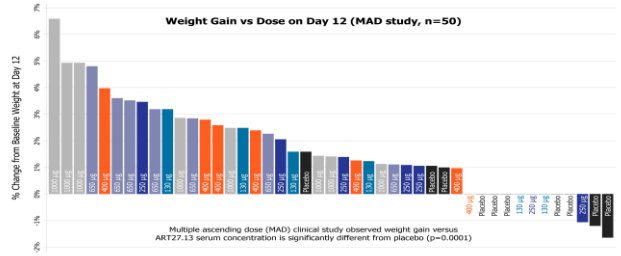
ART27.13[2]
- CB_1 Ki 11 nM (***full*** agonist)
- CB_2 Ki 0.9 nM (***full*** agonist)



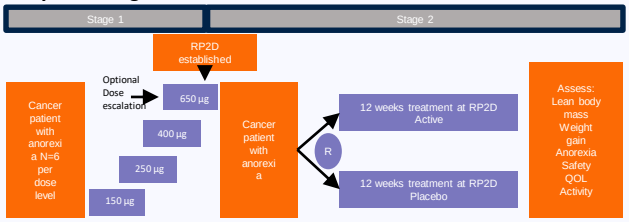
Delta 9-tetrahydrocannabinol (THC)
- CB_1 Ki 5.05 nM2 (***partial*** agonist)
- CB_2 Ki 3.13 nM2 (***partial*** agonist)

Shown as a comparison vs ART27.13

ART27.13 – Observed Weight Gain in Phase 1 Study[1]



Study Flow Diagram



QOL = Quality of Life; R = Randomization; RP2D = Recommended Phase 2 dose
Note: If the 400µg dose group is determined to be safe with sufficient weight gain, the 650µg group will not be evaluated.

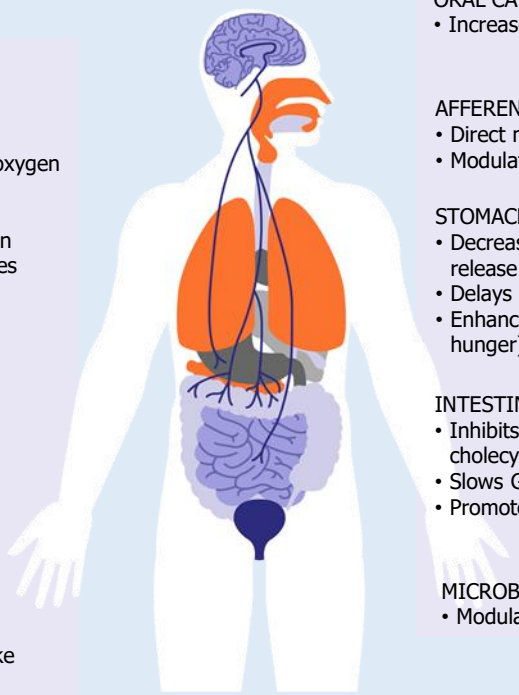
The effects of peripheral CB_1 activation in promoting appetite, food storage and weight gain

FAT TISSUE
- Increases fat cell differentiation
- Increases fat storage
- Decreases mitochondrial respiration and oxygen consumption
- Decreases adiponectin secretion
- Reduces alternative macrophage activation
- Inhibits thermogenesis in brown adipocytes

LIVER
- Increases fatty acid synthesis
- Induces gluconeogenesis
- Promotes liver regeneration

PANCREAS
- Stimulates insulin secretion.
- Reduces insulin-stimulated IR autophosphorylation.
- Can lead to β-cell death.

MUSCLE
- Decreases insulin-mediated glucose uptake
- Regulation of oxidative activity



ORAL CAVITY
- Increases sweet sensitivity

AFFERENT VAGUS NERVE
- Direct modification of gut-brain signalling
- Modulates gastric vagal afferent mechanosensitivity

STOMACH
- Decreases gastric secretion and acetylcholine release.
- Delays gastric emptying
- Enhances ghrelin (a hormone stimulating hunger) release

INTESTINE
- Inhibits secretion of the satiation hormone cholecystokinin
- Slows GI motility
- Promotes western diet preferences

MICROBIOME
- Modulates gut bacteria

DISCUSSION

Anorexia and the resulting weight loss in cancer patients can compromise health, weakening the immune system, causing discomfort and dehydration, ultimately reducing the patient's prognosis and quality of life. ART27.13 represents a novel therapeutic strategy to stimulate appetite and weight gain known to arise from CB_1 receptor activation that could significantly benefit patients with CACS. For the broader community, the data that will arise from this study will help elucidate the potential of modulating the peripheral cannabinoid system in the control of appetite and weight and inform the development strategies for trials targeting this underserved patient group.

Trial registration: EudraCT NUMBER:2020-000464-27. **Research Ethics Committee reference:** 20/NE/0198.

References:
1. Artelo Data on File: Note* 1000 µg dose will not be studied in CAReS & 130 µg dose has been substituted for a 150 µg dose.
2. Schou, M, Varnas K, Jucaite A, Gulyas B, Halldin C, Farde, L Radiolabeling of the cannabinoid receptor agonist AZD1940 with carbon-11 and PET microdosing in non-human primate, N Med Bio 2013;40;3;410-414