MONTELUKAST, A LEUKOTRIENE RECEPTOR ANTAGONIST, FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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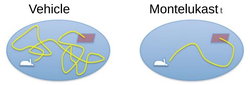
TSX-V: IGX
OTCQX: IGXT

Background

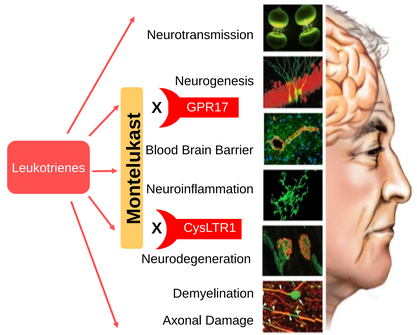
- As modern medicine has improved human life expectancy, cases of age-related cognitive impairment have also become increasingly prevalent.
- As the brain ages it loses its ability to generate new cells, while existing cells lose functionality and the ability to prevent neuroinflammation.
- Furthermore, the aged brain tends to produce higher levels of inflammatory agents such as **leukotrienes**, resulting in neuroinflammation and cognitive impairment.
- There is evidence that leukotriene receptor antagonists, such as **Montelukast sodium**, have the potential to reduce neuroinflammation and restore brain cell function (Marschallinger, Nat. Comm., 2015, 6, Grinde B., Engdahl B., Immunity & Ageing, 2017, 14:20).
- Such treatments can be effective for treating various neurodegenerative diseases and conditions, including Alzheimer's Disease, Parkinson's disease, Lewy Body Dementia, Huntington's disease, spinal cord and brain injuries, and stroke.

Improved learning by **Montelukast** treatment in aged rats in the Morris maze test.



Proposed Mechanism of Action of Montelukast

- **Leukotrienes** are small lipidic mediators of inflammation
- They function through binding to the leukotriene receptors GPR17 and CysLTR1, present in different cell types of the brain.
- Harmful effects associated with leukotrienes include:
  - Disturbed neurotransmission
  - Inhibited neurogenesis
  - Disrupted blood-brain barrier
  - Enhanced neuroinflammation
  - Induced neurodegeneration
  - Disrupted myelin and axons



Montelukast binds to the leukotriene receptors thereby blocking the consequent inflammatory effects.

Aim of Montelukast Oral Film Development

- Our goal is to re-purpose Montelukast as a therapeutic to treat neurodegenerative diseases such as Alzheimer's.
- Reformulating Montelukast into an oral film-based platform so as to improve bioavailability over existing tablets.
- IntelGen$_x$ Corp. specializes in the development and manufacturing of thin film semi-solid pharmaceuticals.
- Using IntelGenx's proprietary VersaFilm technology, APIs can be incorporated into a mucco-adhesive film with several advantages over tablets:
  - Avoid/minimize first pass effects
  - Improved API bioavailability
  - Lower dosing and toxicity
  - Easy swallowing
  - Patience compliance

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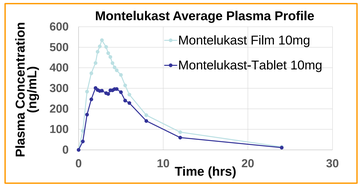
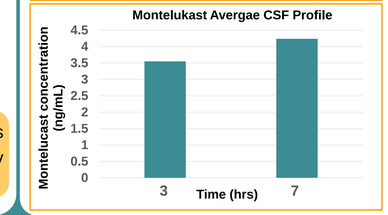
VersaFilm™ Formulations Enhance Active Pharmaceutical Ingredient (API) Uptake Leading to Improved API Bioavailability

- VersaFilm is formulated using a blend of mucco-adhevise polymers which secures the film in close contact with the oral mucosa thereby facilitating oral absorption.
- Dissolution experiments show faster API release from the film platform compared to conventional tablets, allowing faster API dispersal/solubilization and uptake.
- Use of a film-based formulation leads to improved bioavailability and lower toxicity.

Phase I Clinical Study: Plasma and CSF Concentrations

Montelukast-Film in comparison to Montelukast-Tablet (Singulair) at 10 mg in 8 healthy subjects.





- Montelukast-Film has a more than 50% higher bioavailability (area under the curve).
- This finding demonstrates the clear advantage of delivering Montelukast via an oral film.
- For Montelukast to exhibit its therapeutic effect in improving cognitive function, it must cross the blood-brain barrier (BBB).
- Our preliminary clinical studies indicate increasing Montelukast concentrations in the cerebrospinal fluid (CSF) over time.
- The Tmax in CSF is delayed relative to the plasma profile.
- This indicates that Montelukast is able to cross the BBB, and that it is cleared at a slower rate than in plasma.

Phase II Clinical Study:

- Based on Phase 1 Clinical results IntelGenx Corp. has initiated a Phase 2a Montelukast VersaFilm™ proof of concept (POC) clinical trial in Alzheimer's patients, following clearance of the Clinical Trial Application by Health Canada.
- The Phase 2a Montelukast VersaFilm™ clinical trial (NCT03402503) is a randomized, double-blind, placebo controlled POC study that will enroll approximately 70 subjects with mild to moderate Alzheimer's Disease across 8 Canadian research sites.

Primary study objective:

- To evaluate whether 26 weeks of treatment with 10-mg montelukast administered once a day is superior to placebo, assessed at Week 26 using the global Neuropsychological Test Battery (NTB) composite score. This composite score is based on an equally weighted average of standardized change from baseline scores on the ISLT, ISLT-Delay, One Back Test, One Card Learning Test, Verbal Fluency Test, Category Fluency Test, Identification Test and Detection Test.

Secondary study objectives:

- Evaluate whether 26 weeks of treatment with montelukast improved the following:
  - Mini-Mental State Examination (MMSE) score
  - Alzheimer's Disease Cooperative study - Clinical Global Impression of Change (ADCS-CGIC) score
  - Alzheimer's Disease Cooperative study – Activities of Daily Living (ADCS-ADL23)
  - Behavioural disturbances measured by neuropsychiatric inventory (NPI)
  - Bladder Incontinence
- Evaluate whether 6 and 12 weeks of treatment with montelukast is superior to placebo, assessed using the global NTB composite scores as compared to change from baseline
- Evaluate the safety, feasibility, and tolerability of montelukast film, as measured by treatment-emergent adverse events, and changes in laboratory values, vital signs, liver and cardiac parameters

Subject population (key entrance criteria):

- Mild to moderate AD
- MMSE score 14 to 22
- ≥50 years of age
- On treatment with donepezil, rivastigmine or galantamine for ≥3 months
- Not on memantine at least 2 months prior to screening
- Identified caregiver

Analysis Datasets:

- *Full Analysis Set* - all patients who received at least one dose of study medication, and had a baseline (if applicable for the endpoint being analyzed) and post-baseline observation for the measurement of interest.
- *Per Treatment Analysis Set* - have received at least 80% of the protocol prescribed study medication during the interval of the analysis.
- *Safety Analysis Set* - All patients with at least one dose of study medication

Conclusions

- Montelukast-Oral Films exhibit increased bioavailability compared to the Montelukast-tablet.
- Montelukast accumulates in the CSF.
- Given the inherent attributes of Montelukast VersaFilm, this might be a novel effective therapeutic and treatment modality as part of the armamentarium against Alzheimer's Disease.