Plinabulin-Associated Neutrophil Demargination : Evidence for a Clinically Relevant Mechanism of Action for the Prevention of Chemotherapy-Induced-Neutropenia

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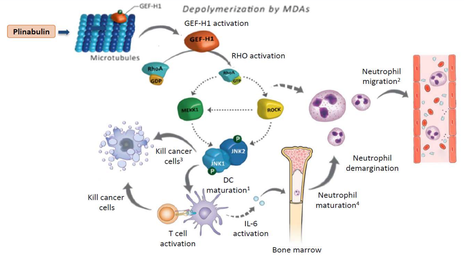
Study BPI-2358-105 (NCT03102606): Phase 2/3, Multicenter, Randomized, Double Blind Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy

Plinabulin Overview:
- **Small Molecule**
- **Inexpensive to manufacture**
- **Given by IV infusion, on the same day of the chemotherapy**
- **More than 300 Patient Data from Phase I,II,III**
- **Currently in Phase III in NSCLC**

- Plinabulin is an Anti-Cancer agent, currently in Development for Non-Small Lung Cancer (NSCLC) (ASCO-SITC 2017)
- Plinabulin is also under development for the prevention of Chemotherapy-Induced Neutropenia (CIN)
- Plinabulin is a small molecule activator of GEFH1,and represents a novel signaling pathway leading up to activation of Dendritic Cells, resulting in Interleukin-6 (IL-6) production
- **IL-6 has been shown to induce Neutrophil Demargination and to shorten Neutrophil Transit Time from Bone Marrow (Suwa et al, Am J Physiol 2000;279:H2954-H2960**



➢ **Plinabulin Activates Dendritic Cells, leading to IL-6 Production**

➢**IL-6 Induces Neutrophil Demargination**

➢ **IL-6 shortens Neutrophil Transit Time from the Bone Marrow**

Methods

Objective:

To obtain evidence of Neutrophil Demargination and Neutrophil Transit Time shortening with Plinabulin.

- Since patients also received Dexamethasone (which is known to induce Neutrophil demargination), we analyzed the effects of incremental doses of Plinabulin against a fixed back ground dose of Dexamethasone, thus with Plinabulin dose being the only variable.

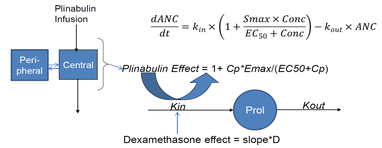
Method:

- We analyzed the effect of Plinabulin on Absolute Neutrophil Count (ANC) changes in two different ways: 1. By a nonlinear mixed effects PK/pharmacodynamic (PD) modeling to determine if Plinabulin's effects on ANC turnover (production and clearance) were additive to Dexamethasone, and 2. By comparing the dose-dependant increase in ANC of Plinabulin on Day 2 vs Day 1 predose (=baseline without Plinabulin).
  - For PK/PD modeling, data was available from 41 pts; 27 pts with Dexamethasone, Docetaxel and Plinabulin (at the different dose levels 5,10 and 20 mg/m2 Plinabulin), and 14 subjects with Dexamethasone and Docetaxel, but without Plinabulin (= 0 mg/m2 Plinabulin).
    - Plinabulin doses were 0 (n=14), 5 (n=14), 10 (n=13) or 20 (n=14) mg/m2 in NSCLC patients
    - Plinabulin was administered on Day 1, 30 minutes after Docetaxel
    - Dexamathasone (16 mg/day) was given on Day 0, 1, and Day 2.
  - ANC was taken at predose D1 (prior to Docetaxel and Plinabulin administration) and D2, D5,D6,D7,D8,D9,D10, and D15.
  - Blood sampling for Plinabulin pharmacokinetics (PK) was obtained before and at specified intervals after Plinabulin dosing on D1.
  - **Demargination was defined as: The increase in ANC on Day 2 (24 hour after Plinabulin dose) vs Day 1:**
    - The Day 2 increase in ANC vs Day 1 was considered a specific Plinabulin effect, since the Dexamethasone dose was constant on Day 0,1 and 2
    - N nadir occurred around Day 9.

Results

PK/PD Modeling Results

Figure 1. PK/PD Turnover Model



Kin = Rate of production (or turnover) of neutrophils
Kout = fractional turnover rate neutrophils
Baseline steady state level of effect = *Kin/Kout* (without drug, system is at steady state)
Turnover time of system = *1/Kout*
Emax is a fractional increase in *Kin* over baseline
Observed Effect =1+ Plinabulin Effect + Dexamethasone Effect
D is the unobserved dexamethasone concentration; Slope*D is estimated as a constant

Figure 2. Pre-Treatment Absolute Neutrophil Count (ANC)

Key Finding:

1. Pretreatment ANC was comparable in the groups receiving Dexamethasone alone (without Plinabulin) and Dexamethasone + Plinabulin

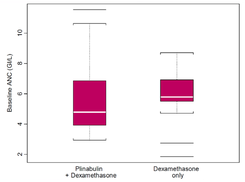
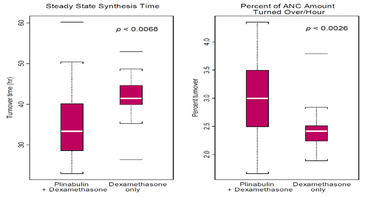


Figure 3. The addition of Plinabulin to Dexamethasone significantly alters ANC K-in and K-out versus Dexamethasone alone

Key Findings:

1. Plinabulin significantly shortens Steady State Synthesis Time (K-in), thus release of ANC into the systemic circulation
2. Plinabulin significantly increases clearance on ANC from the systemic circulation (K-out)



ANC Demargination Results

Figure 4. Baseline ANC for Different Plinabulin Dose Groups

Key Finding:

1. Baseline ANC was comparable for all Plinabulin dose groups

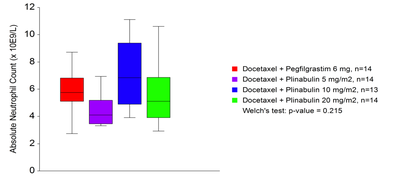


Figure 5. ANC Demargination for Different Plinabulin Dose Groups

Key Finding:

1. Increased ANC Demargination with Increasing Plinabulin Doses

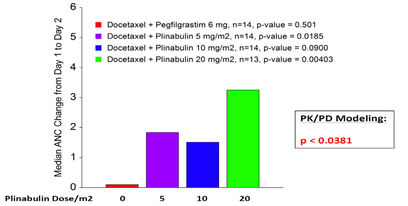
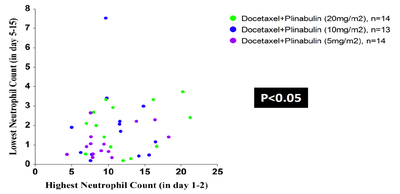


Figure 6. The Higher ANC Demargination on Day 2 the Higher ANC Nadir during Cycle 1

Key Finding:

1. ANC Demargination protects against Neutropenia in Cycle 1



Plinabulin vs. Pegfilgrastim

Table 1. Plinabulin Superior Profile compared with Pegfilgrastim

Target Indication: Prevention of all chemo-induced neutropenia in all cancers

For Patients
- **High Quality of Life** (less bone pain)
- **Ease of Use** (first day dosing)

For Physicians
- **Potential for Improved Efficacy** (durable anti-cancer benefit, more chemo cycles of treatment)
- **Potentially Fewer ER Visits**

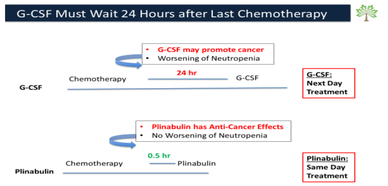
For Payers
- **Lower cost** with lower hospitalization admissions rate and duration of stay
- **Maintain pricing similar to G-CSFs**

For Production
- **Potential for large commercial opportunity** in an already-established and underserved market
- **Opportunity for significantly lower COGs** (small molecule vs. biologic)

Compelling Safety Profile To-Date

Plinabulin AEs: nausea, vomiting, diarrhea, and transient hypertension

G-CSF AEs: bone pain, splenic rupture and splenomegaly, acute respiratory distress syndrome, glomerulonephritis, and capillary leak syndrome



Conclusion

- **Plinabulin, an equally effective, single-dose-per cycle agent for CIN, has a different Mechanism of Action versus G-CSF**
- **Neutrophil Demargination and Shortening of Synthesis Time are clinically relevant Mechanisms of Action with Plinabulin**
  - **This is consistent with the known IL-6 signaling in Neutrophil Biology**
  - **Plinabulin's known IL-6 Release from Dendritic Cells is consistent with the observed Neutrophil Demargination and Shortening of Neutrophil Synthesis Time**

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