# Pharsight
A Certara™ Company

# Pharmacokinetic Analysis of β-Glucan After Administration of PGG-Glucan, a Novel Immunomodulator Being Developed for the Treatment of Non-Small Cell Lung Cancer

JF Marier[1], C Jomphe[1], M Beliveau[1], JR Lowe[2], P Mattson[2], R Walsh[2], and ML Patchen[2]

[1]Pharsight Consulting Services, Montreal, Canada[1], [2] Biothera, Eagan, Minnesota, USA.

BIOTHERA
the immune health company

## BACKGROUND

Biothera is developing an intravenous (i.v.) formulation of Imprime PGG® Injection (Imprime PGG), a proprietary, soluble, yeast-derived b-1,3/1,6 glucose polymer, for the treatment of cancer in combination with monoclonal antibody (mAb) therapy.

- Imprime PGG binds and activates complement receptor 3 (CR3) on innate immune cells (neutrophils and monocytes), directing these cells to kill tumor cells that have been opsonized by iC3b following targeting by anti-tumor mAbs.
- This type of cytotoxicity has been referred to as CR3-dependent cell-mediated cytotoxicity (CR3-DCC) and differs from traditional antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).
- Binding of Imprime PGG to neutrophils and monocytes is complement-dependent. In humans, naturally occurring anti-beta glucan antibodies (ABA) are required for binding of Imprime PGG to these innate immune cells. Biothera has discovered that there are minimum ABA levels necessary for this binding. An emzyme-linked immunosorbent assay (ELISA) for measuring serum ABA has been developed to quantitatively identify subjects with ABA levels conducive for Imprime PGG binding to innate immune cells ("biomarker positive") vs others ("biomarker negative").
- Numerous studies in syngeneic and human xenograft tumor models in mice have demonstrated that administration of Imprime PGG in combination with anti-tumor mAb treatment reduces tumor growth and extends long-term survival beyond that observed with either agent alone. Thus, Imprime PGG in combination with mAb therapy has the potential to enhance the efficacy of these targeted therapies in man.

A Phase 2 study of Imprime PGG in combination with the anti-tumor mAb, cetuximab, was performed in 90 subjects with previously untreated Stage IIIb or IV non-small cell lung cancer (NSCLC) to assess potential drug-drug interaction between Imprime PGG, cetuximab, paclitaxel and carboplatin.

## METHODS

BT-CL-PGG-LCA0822 was a randomized, Simon two-stage, open-label, multicenter, efficacy and safety Phase 2 study.

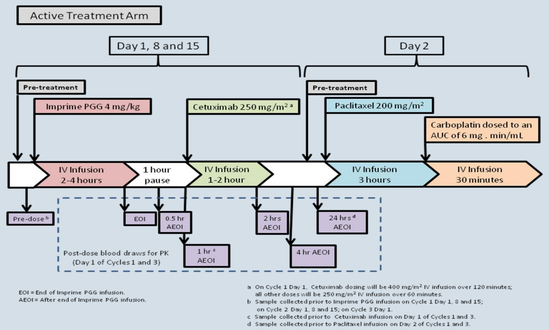
The study was conducted as a two-arm design with the intention of assessing the initial efficacy and safety of Imprime PGG in the treatment of NSCLC.

- The aim of the first stage was to enroll approximately 22 evaluable subjects across both arms (approximately 15 into the active treatment arm and 7 into the active control arm).
- When the criteria for progression to the second stage were met, approximately 68 additional subjects were enrolled into the second stage giving a total enrollment of 90 evaluable subjects.
- Each treatment cycle was 3 weeks in duration. During each cycle, cetuximab alone (active control arm) or Imprime PGG and cetuximab (active treatment arm) were dosed during all 3 weeks on Days 1, 8 and 15. In both the active treatment arm and the active control arm, dosing of paclitaxel and carboplatin occurred on Day 2 of each cycle and may have been stopped at the discretion of the investigator following completion of at least Cycle 4 dosing, but had to be stopped after completion of Cycle 6 dosing.

## METHODS

Figure 1 displays the dosing and PK sampling times.

**Figure 1: Schedule of Active Treatment Arm Dosing and PK Sampling**




EOI = End of Imprime PGG infusion.
AEOI = After end of Imprime PGG infusion.

a On Cycle 1 Day 1, Cetuximab dosing will be 400 mg/m² IV infusion over 120 minutes; all other doses will be 250 mg/m² IV infusion over 60 minutes.
b Sample collected prior to Imprime PGG infusion on Cycle 1 Day 1, 8 and 15; on Cycle 2 Day 1, 8 and 15; on Cycle 3 Day 1.
c Sample collected prior to Cetuximab infusion on Day 1 of Cycles 1 and 3.
d Sample collected prior to Paclitaxel infusion on Day 2 of Cycles 1 and 3.

**Active Treatment Arm:**

| | |
|---|---|
| Day 1 | Imprime PGG 4 mg/kg, i.v., over 2 to 4 hours + Cetuximab 250* mg/m², i.v., over 1 hour |
| Day 2 | Paclitaxel 200 mg/m², i.v., over 3 hours + Carboplatin dosed to an AUC of 6 mg.min/mL based on the Calvert formula (i.v., over 30 minutes) |
| Day 8 & 15 | Imprime PGG 4 mg/kg, i.v. over 2 to 4 hours + Cetuximab 250 mg/m² i.v., over 1 hour |

**Active Control Arm:**

| | |
|---|---|
| Day 1 | Cetuximab 250* mg/m², i.v., over 1 hour |
| Day 2 | Paclitaxel 200 mg/m², i.v., over 3 hours + Carboplatin dosed to an AUC of 6 mg.min/mL based on the Calvert formula (i.v., over 30 minutes) |
| Day 8 & 15 | Cetuximab 250 mg/m² i.v., over 1 hour |

* Initial cycle Day 1 dose was given at 400 mg/m², i.v., over 2 hours; all other doses were given at 250 mg/ m², i.v., over 1 hour

- For subjects receiving Imprime PGG treatment, serial blood samples were collected Day 1 of Cycles 1 and 3 (see times on Figure 1) and trough samples collected weekly between these days.
- Serum concentrations of β-glucan were measured with an enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation (LOQ) of 0.0047 µg/mL.
- Pharmacokinetic (PK) analysis of β-glucan was performed using noncompartmental methods.

## RESULTS

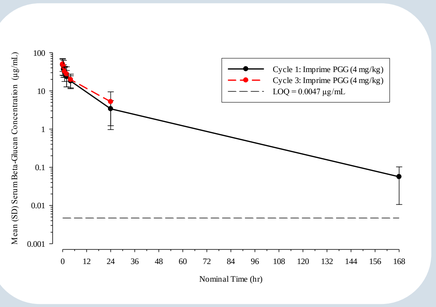
Descriptive statistics of PK parameters of beta-glucan are presented in Table 1 and mean (±SD) concentration-time profiles are presented in Figure 2.

**Table 1. Summary of β-Glucan PK Parameters - Cycle 1/Day 1 and Cycle 3/Day 1**

| Parameters | Geometric Mean (CV%) - 4 mg/kg Imprime PGG (with cetuximab, paclitaxel and carboplatin) | |
|---|---|---|
| | Cycle 1 / Day 1 | Cycle 3 / Day 1 |
| N | 52 | 36 |
| $AUC_{0\text{-last}}$ (µg•hr/mL) | 605 (55.3) | 396 (38.1) |
| $AUC_{0\text{-}24}$ (µg•hr/mL) | 362 (35.2) | 396 (34.8) |
| $AUC_{0\text{-}\infty}$ (µg•hr/mL) | 621 (53.1) | 416 (30.4) |
| $C_{max}$ (µg/mL) | 44.3 (34.9) | 47.8 (37.3) |
| CL (L/hr) | 0.477 (46.4) | 0.696 (32.1) |
| $t_{1/2}$ (hr) | 19.1 (42.8) | 8.46 (23.2) |
| $T_{max}$ [a] (hr) | 2.25 (1.97, 4.33) | 2.40 (1.93, 4.17) |
| $V_{ss}$ (L) | 6.60 (35.5) | 6.48 (39.9) |

[a] = Median (min, max)

**Figure 2: Mean (±SD) Concentration Profiles of β-Glucan Cycle 1/Day 1 and Cycle 3/Day 1**




- Mean $AUC_{0\text{-}24}$ values of β-glucan in Cycle 1 and Cycle 3 parameters were similar (362 and 396 µg.hr/mL, respectively).
- Likewise, mean $C_{max}$ values of β-glucan in Cycle 1 and Cycle 3 parameters were similar (44.3 and 47.8 µg/mL, respectively). Median $T_{max}$ values in Cycle 1 and Cycle 3 were observed at 2.25 and 2.40 hr, respectively. Overall, the above results suggest that the exposures to β-glucan in Cycle 1 and Cycle 3 were similar.
- Results for $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, CL and $t_{1/2}$ should be interpreted with caution considering the shorter blood sampling interval in Cycle 3 (i.e., 24 hr) as opposed to Cycle 1 (i.e., 168 hr).
- Mean trough concentrations of β-glucan on Day 22 (Day 1, Cycle 2) and Day 43 (Day 1, Cycle 3) were 0.0680 and 0.117 µg/mL, respectively. The increase in β-glucan concentrations across cycles was not considered clinically relevant considering the range of concentrations observed in the current study and $C_{max}$ values.

A biomarker predictive of Imprime PGG clinical response (positive or negative) was previously identified. An exploratory analysis was performed to assess potential relationships between the biomarker status and PK. Descriptive statistics of PK parameters of β-glucan by biomarker status are presented in Table 2.

**Table 2: Summary of β-Glucan PK Parameters Stratified by Biomarker Status - Cycle 1/Day 1 and Cycle 3/Day 1**

| Parameters | Geometric Mean (GeoCV%) - 4 mg/kg Imprime PGG (with cetuximab, paclitaxel and carboplatin) | | | |
|---|---|---|---|---|
| | Cycle 1 / Day 1 | | Cycle 3 / Day 1 | |
| | Biomarker Positive | Biomarker Negative | Biomarker Positive | Biomarker Negative |
| N | 19 | 33 | 12 | 24 |
| CL (L/hr) | 0.453 (51.1) | 0.492 (44.0) | 0.625 (39.4) | 0.731 (28.3) |
| $V_{ss}$ (L) | 6.09 (33.7) | 6.92 (36.1) | 6.63 (32.9) | 6.41 (44.0) |

- Geometric mean CL values of β-glucan in Cycle 1 and Cycle 3 parameters were similar when comparing subjects with positive and negative Imprime PGG biomarker status.
- Likewise, mean $V_{ss}$ values were similar in positive and negative biomarker status.

## CONCLUSIONS

- Paclitaxel and carboplatin did not have a residual effect on the PK of b-glucan following administration of Imprime PGG in combination with cetuximab in patients with NSCLC. The expected added efficacy of combining Imprime PGG with cetuximab in patients with NSCLC is not due to a higher exposure to b-glucan secondary to a drug-drug interaction.
- Minimal accumulation of β-glucan was observed since trough concentrations on Day 1/Cycle 2 and Day 1/Cycle 3 were 0.0680 and 0.117 µg/mL, respectively.
- Mean PK parameters of β-glucan were similar in patients with positive and negative Imprime PGG biomarker status in Cycle 1 and Cycle 3. In addition, results were also similar when comparing to the overall population. These results suggest that the biomarker status did not affect the PK of b-glucan.