Modeling and Simulations of a Novel Beta-Glucan Biologic Administered Alone or in Combination with Cetuximab, with and without Irinotecan in Colorectal Cancer Patients

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BACKGROUND

Biothera is developing an intravenous (i.v.) formulation of Imprime PGG® Injection (Imprime PGG), a beta 1,3/1,6 glucose polymer

- β-glucans are polymers of glucose that are extractable from yeasts, fungi (mushrooms), seaweed, and some cereals.
- In nature, yeast can trigger an anti-yeast cytotoxic response not only by innate immune cells such as natural killer cells and macrophages, but also by neutrophils.
- A prerequisite to this cellular response is activation of the complement cascade. This leads to opsonization (coating) of the yeast cells with the inactivated form of complement component 3b (iC3b), a relatively early component in the complement cascade.
- Cytotoxic activity is then mediated via interactions with complement receptor 3 (CR3) on innate immune cells. When such dual ligation of CR3 is engaged, the effector cells, in particular neutrophils, exert cytotoxic responses against the opsonized target.
- This type of cytotoxicity has been referred to as CR3-dependent cell-mediated cytotoxicity (CR3-DCC) and differs from traditional antibody dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Imprime PGG in combination with cetuximab has the potential to enhance the efficacy of this targeted therapy in man.

Imprime PGG was administered alone in healthy subjects in a Phase I study, and in combination with cetuximab with or without irinotecan in patients in patients with colorectal cancer (CRC) in a Phase 1b/2 study.

The goal of this project was to perform PK modeling of β–glucan to support dosing rationale of imprime PGG and assess potential drug-drug interactions with cetuximab, with and without irinotecan treatments.

METHODOLOGY

Phase 1 Study in Healthy Subjects (BIOBG-CL-001)

- This was a Phase 1, single-center, randomized, double-blind, placebo-controlled, dose-escalation study of Imprime PGG administered by 1- to 3-hour infusion to healthy subjects.
  - The study was designed to obtain information about the safety, pharmacodynamics, and pharmacokinetics of a single dose of Imprime PGG over a range of potentially therapeutic doses.
  - The study consisted of a 2-week screening period, a 1-day treatment period, and a 1-week follow-up period.
  - For each single-dose treatment group, three subjects were randomized to Imprime PGG (doses ranging from 0.5 to 6 mg/kg), and one subject was randomized to placebo.
- The mean age of healthy subjects was 25.1 years of age. A total of 13 healthy subjects were male (72.2%), and 5 (27.8%) were female.

METHODOLOGY

Phase 1b/2 Study in Patients with Colorectal Cancer (BT-CL-PGG-CRC0713)

- The safety, pharmacokinetics, and efficacy of Imprime PGG® in combination with cetuximab with or without concomitant irinotecan therapy was evaluated in subjects with recurrent or progressive colorectal carcinoma following treatment with a 5-fluorouracil-containing regimen (clinical).
- Imprime PGG was administered in the following sequential treatment arms:
  - Arm 1: Imprime PGG and standard doses of cetuximab and irinotecan (n=10)
  - Arm 2: Imprime PGG and standard doses of cetuximab only (n=22).
- Subjects were treated in 6-week cycles, with irinotecan administered weekly for Week 1 through Week 4 and Imprime PGG and cetuximab administered weekly for Week 1 through Week 6.
- On Day 1 of Cycle 1 (Cycle 1/Day1) and on Day 1 of Cycle 2 (Cycle 2/Day 1), blood samples for PK assessments were drawn prior to Imprime PGG dosing, at the end of Imprime PGG dosing, and at the following timepoints: 0.5, 1, 2, 4, 8 and 24 hr after the end of Imprime PGG dosing.
- Blood samples for PK assessments were also drawn prior to Imprime PGG dosing on all other weeks of Cycle 1 and Cycle 2 (i.e, Days 8, 15, 22, 29 and 36).

Imprime PGG Dosing Information in Healthy Subjects and Cancer Patients

Imprime PGG Dose (mg/kg)	Healthy Subjects	Cancer Patients	Infusion Volume (mL)	Infusion Time (hr)	Imprime PGG Concentration (mg/mL)[1]	Rate of Infusion (mg/min)[1]
0.5	Yes	No	250	1	0.15	0.63
1.0	Yes	Yes	250	1	0.3	1.25
2.0	Yes	Yes	250	1	0.6	2.50
4.0	Yes	No	500	1	0.6	5.00
5.0	Yes	Yes	500	2	0.6	2.50
6.0	Yes	No	750	3	0.6	2.50

Bioanalytical Assay

- β-glucan serum concentrations were measured with an enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation (LOQ) of 0.0047 µg/mL.
- A total of 2933 measurable plasma concentrations of β-glucan (>BLQ) were available from 144 subjects in Phase Ia and Ib studies.

Modeling and Simulations

- Population pharmacokinetic (PK) modeling of β-glucan was performed to assess sources of variability and potential drug-drug interactions (DDI).
- Simulations were performed to assess the extent of accumulation following repeated dosing and evaluate the contribution of the elimination half-life associated to the α, β, and γ phases to the overall accumulation of the product.
- Modeling and simulations were performed with Phoenix NLME (V1.3).

KRAS Gene Mutation

- The presence of a KRAS gene mutation in a subject's colorectal tumor has been shown to be predictive of a lack of response to cetuximab therapy8.
- Potential relationship between KRAS gene mutation (reported as wild type, mutant, or unknown) and PK parameters of β-glucan were explored.

RESULTS

Figure 1. Concentration-Time Profiles of β-Glucan in Healthy Subjects (Panel A) and Patient with CRC in Cycle 1 and 2 (Panel B and C, respectively)

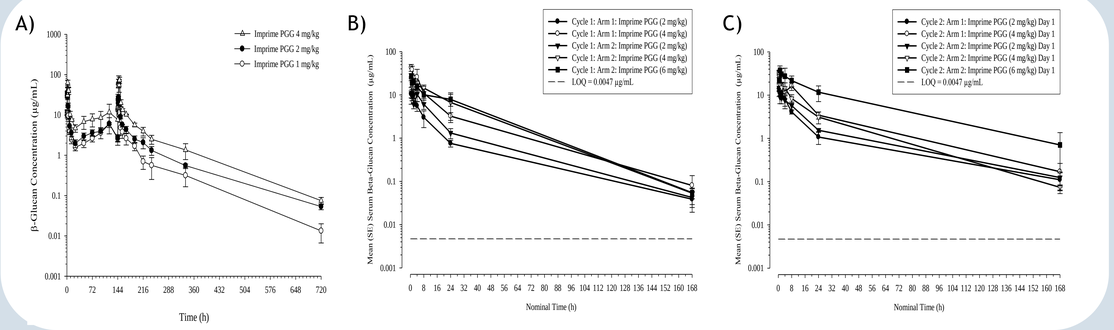

Table 2. Summary of β-Glucan Pharmacokinetics in Healthy Subjects and Patient with Colorectal Cancer

Populations	Concomitant Treatment	Geometric Mean (CV%)					
		CL (L/h)	Vc (L)	Vss (L)	t1/2α (h)	t1/2β (h)	t1/2γ (h)
Healthy Subjects (n=26)	None	0.491 (16.8)	4.94 (37.4)	TBD (TBD)	2.68 (33.3)	27.3 (50.8)	9098 (26.5)
Cancer Patients (n= 10)	Cetuximab and Irinotecan	0.565 (38.5)	7.39 (36.2)	TBD (TBD)	3.38 (28.7)	24.2 (52.3)	7803 (56.3)
Cancer Patients (n= 22)	Cetuximab	0.690 (27.2)	10.8 (35.9)	TBD (TBD)	3.73 (34.2)	19.5 (37.1)	11340 (49.3)

CL = Systemic clearance, Vc = Central volume of distribution, Vss = Total volume of distribution, $t_{1/2}\alpha$ = elimination half-life associated to the α phase, $t_{1/2}\beta$ = elimination half-life associated to the β phase, $t_{1/2}\gamma$ = elimination half-life associated to the γ phase, CV% = coefficient of variation.

- A 3-compartment model with linear elimination was used to model concentration-time profiles of β-glucan. The model resulted in adequate goodness of fit.
- Typical systemic clearance (CL) of β-glucan in healthy subjects or cancer patients treated with cetuximab or cetuximab and irinotecan were 0.491, 0.565, and 0.690 L/h, respectively. No DDI was observed following co-administration of the novel β-glucan biologic, with cetuximab or cetuximab and irinotecan.
- The effective half-life (t1/2) contributing to the accumulation of β-glucan ranged from 19.5 to 27.3 h, respectively.
  - The intermediate ß phase was identified as the most important component describing the overall exposure in terms of AUC of ß-Glucan.
  - Therefore, the "effective" half-life was considered to be adequately represented by $t_{1/2ß}$, with values among the healthy, Arm 1 and Arm 2 subjects ranging from 19.5 to 27.3 h and achievement of steady state within approximately 5 days.
  - Based on the observed $t_{1/2ß}$, a 7-day (once-weekly) dosing interval will be expected to result in negligible ß-Glucan accumulation in healthy subjects and cancer patients, whereas shorter dosing intervals (e.g., bi-weekly or every 48 h) would lead to noticeable accumulation.
- No significant differences were observed in PK parameters in KRAS subgroups.

CONCLUSIONS

- Typical CL of β-glucan in cancer patients treated with cetuximab or cetuximab and irinotecan were similar. No DDI was observed following co-administration of the novel β-glucan biologic, with cetuximab or cetuximab and irinotecan.
- The effective half-life ($t_{1/2}$) contributing to the accumulation of β-glucan ranged from 19.5 to 27.3 h, respectively. Repeated dosing is expected to result in negligible accumulation β-glucan.
- KRAS status did not appear to influence the pharmacokinetics of Imprime PGG in colorectal cancer patients.
- The above population PK model is being used to support dosing of β-glucan in cancer patients in other Phase II studies.