Interim results of a novel 10% liquid intravenous immune globulin (IVIG) product's Phase III Prospective, Open-Label Multicenter Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics in Adults and Children with Primary Immunodeficiency Disease (PIDD)

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Introduction

Background

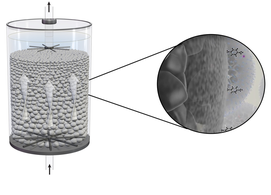
PlasmaCap™ IG is a 10% liquid formulation intravenous immune globulin (IVIG) product manufactured from US source plasma. The product is indicated for replacement therapy in primary immune deficiency diseases (PIDD) in patients two years of age and older. The clinical trial was initiated in 2017 in both the United States and Canada. The purpose of this study is to investigate the efficacy, safety, tolerability, and pharmacokinetic profile of PlasmaCap IG.

The adult portion of the trial was completed in February 2019 and the pediatric portion is expected to be completed in November 2020. Presented here is unofficial data. PlasmaCap IG is the first plasma derived product manufactured using PlasmaCap EBA technology.

PlasmaCap IG is manufactured using a novel protein extraction method

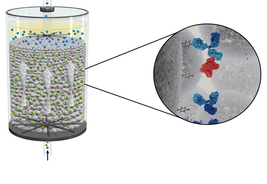
PlasmaCap EBA® technology uses expanded bed adsorption (EBA) chromatography to selectively capture proteins in their native state, and in many cases, at a higher yield per liter of plasma (compared to published industry norms using traditional cold ethanol fractionation)[1]. PlasmaCap EBA selectively captures target proteins, and does not involve precipitation, potentially resulting in more consistent quality and purity when compared to conventional fractionation methods. The process does not use ethanol precipitation, and processing steps are performed at room temperature without the freeze/thaw of intermediate product fractions. These processing steps are performed under conditions which conserve the molecular structure of IgG.

The chromatography column works through 3 major steps, Equilibration, Loading and Elution (**Figure 1-3**).



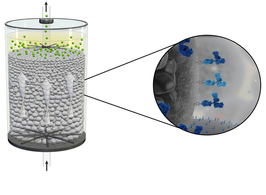
Equilibration

Figure 1. EBA columns are expanded by flowing liquid upward through the column and equilibrated to condition the ligand for optimal binding of IgG.



Load

Figure 2. Columns are loaded by flowing plasma upward, exposing the ligand to all plasma proteins.



Elution

Figure 3. The IgG molecules are unbound from the column, flowing upwards from the flow of elution buffer.

Capture of native IgG from plasma is made possible by creating a stable fluidized bed that is not affected by the variability in lipid, lipoproteins, micelles, and soluble aggregates that have made previous attempts to directly capture IgG by chromatographic methods unsuccessful.

EBA columns operate in upward flow allowing plasma to be processed without aggressive cleaning, sanitizing, and conditioning agents, and with little risk of plugging. Tungsten-carbide agarose beads allow for highly precise, native extraction **(Figure 4)**.

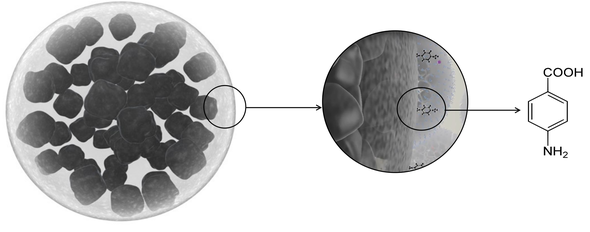


Figure 4. Tungsten-carbide agarose beads with 4-aminobenzoic acid ligands selectively bind the Fc portion of IgG by isoelectric attraction, hydrogen bonding, van der waals forces, π-π stacking, π-cation, aromatic ring, and hydrophobic interactions.

PlasmaCap IG

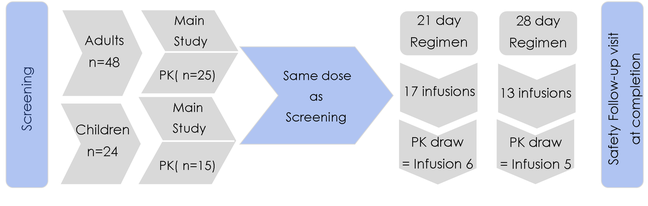
Attribute	Average	n
Recovery*	68.7 ± 2.5	21
IgG monomer plus dimer	99.5 ± 0.3%	34
Fc function	30 mg: 111 ± 14%	10

Table 1: PlasmaCap IG product attributes

** Recovery represents Clinical Scale Manufacturing and is expected to improve at Commercial scale*

Clinical Trial Methods

Clinical Trial Identifier #NCT03238079



Study Outcome Measures

Efficacy:

Primary: Mean annual acute serious bacterial infections (SBIs) is significantly less than 1/subject/year.

Secondary:

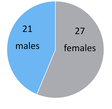
- Average serum IgG trough concentration prior to each infusion
- Number of: infection episodes (serious and non-serious), days missed of work/school/daycare or, days unable to perform normal daily activities due to infections, days of hospitalizations due to infections, episodes of fever, use of antibiotics to treat infection and short-term prophylaxis prior to and following surgical and dental procedures
- Ability of the Investigational Medicinal Product to maintain stable, therapeutic IgG levels

Safety: Adverse Events(AEs), viral safety, monitor for hemolysis and thromboembolic events.

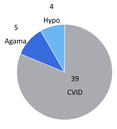
Pharmacokinetic: Determine the PK profile plasma concentration-time curve and half life ($t_{1/2}$) for each phase of the curve.

Results

Adults



Gender



Diagnosis

	Age	Weight	Dose/Infusion
Average	49	88kg	552mg/kg
Range	20-70	53-132kg	300-840mg/kg

Children

Age	Gender
12	F
6	M
16	F
11	F
8	M
7	M
4	M
11	F
11	M
7	M
16	M
14	M

Diagnosis

	Weight	Dose/Infusion
Average	39kg	495mg/kg
Range	20.5-101.6kg	371-690 mg/kg

The Adult portion of the study completed with a total of 661 infusions. 42 Adults completed the study and 6 withdrew between visits 3 and 6, three for personal reasons (n=3), one due to generalized pruritus (n=1), and two due to unrelated AEs: aseptic meningitis (n=1) and colon cancer (n=1)). All adult doses completed without the use of pre-medication. 96.25% of the 613 adult infusions and 95.75% of the 141 children's infusions to date were completed without slowing, interrupting, or stopping the infusion. As of June 2019, 12 children were enrolled in the study and have completed 92 infusions.

Efficacy:

There were no Serious Bacterial Infections (SBIs) or study drug related Serious Adverse Events (SAEs).

Safety:

There were no reports of viral transmissions, hemolysis or thrombosis events.

Most Frequent Related AEs	No. (%) of subjects (N=59)	Mild	Moderate	Severe
Headache	24 (41%)	17	6	1
Increased BP	8 (14%)	3	0	0
Fatigue	10 (17%)	7	3	0
Others	33 (56%)	24	7	2

Table 2: Unofficial safety data of the most frequent product related Adverse Events (AEs)

Pharmacokinetics:

27 Adults participated in the PK portion of the study. The preliminary adult PK parameters obtained (Table 3) are similar to those reported with the other licensed IVIG preparations. Of the 12 enrolled children, 9 are enrolled in the PK portion of the study.

Adult PK Parameter	Unit	Average (SD)
AUC(0-t)	(hr*mg/mL)	1933 (869)
AUC(0-Inf)	(hr*mg/mL)	2460 (908)
Cmax	(mg/mL)	13.64 (5.20)
Tmax	(hr)	1.57 (1.48)
t1/2	(hr)	184 (122)
CL	(mL/hr)	73 (130)
Vss	(L)	11.4 (8.9)

Table 3: Unofficial adult Pharmacokinetic (PK) data

Discussion/Conclusions

This preliminary data for adults and ongoing data for children, appear to indicate that PlasmaCap IG is efficacious, safe, and well tolerated in the treatment of patients with PIDD with no SBIs or related SAEs to date.

References

1- Radosevich, M., and T. Burnouf. "Intravenous Immunoglobulin G: Trends in Production Methods, Quality Control and Quality Assurance." *Vox Sanguinis*, vol. 98, no. 1, 2010, pp. 12–28., doi:10.1111/j.1423-0410.2009.01226.x.