Interim Safety Data in a Prospective, Open-Label, Multi-Center Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of PlasmaCap IG in Patients with Primary Immunodeficiency Diseases (PIDDs)

Dr. Richard L. Wasserman, MD PhD FAAAAI, Allergy Partners of North Texas, Dallas, TX; Jacinthe Guindon, MSM, Evolve Biologics, Mississauga, Canada

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 US and Canada. The purpose of this study was to investigate the efficacy, safety, tolerability, and pharmacokinetic profile of PlasmaCap IG.

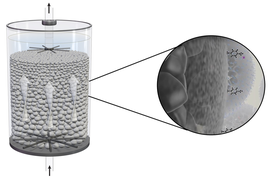
The trial was completed in February 2019 for adults and is expected to be completed in November 2020 for children. Data presented here is as of the most recent safety review, completed in November 2018.

PlasmaCap IG is the first plasma derived product manufactured using PlasmaCap EBA™ technology. Key Opinion Leaders(KOL) were interviewed to make sure the optimal formulation was designed.

PlasmaCap IG and PlasmaCap EBA™

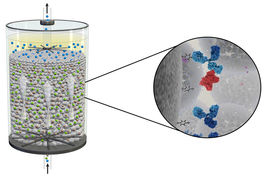
PlasmaCap EBA is a novel protein extraction method. The technology uses expanded bed adsorption (EBA) chromatography to selectively capture proteins in their native state, and in many cases, at a higher yield from each liter of plasma (compared to published industry norms using traditional cold ethanol fractionation)[1]. Direct chromatographic capture of IgG from plasma selectively isolates specific proteins without affecting the protein structure, resulting in potentially more consistent quality and purity when compared to conventional methods such as cold ethanol fractionation. 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 higher order structure of IgG.

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



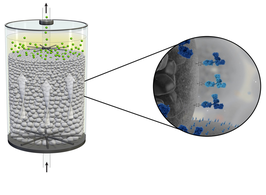
Equilibration

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 or fouling. Tungsten-carbide agarose beads allow for highly precise, native extraction (**Figure 4)**.

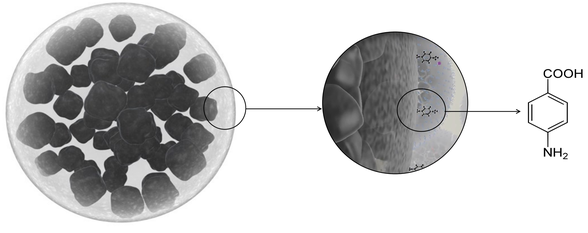
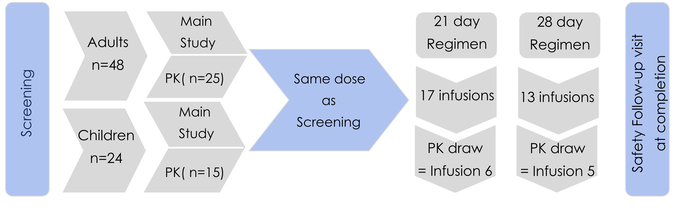


Figure 4. Tungsten-carbide agarose beads with 4-aminobenzoic acid ligands selectively bind the Fc portion of IgG by isoelectric attraction, hydrogen bonding, van der waals forces, π-π stacking, π-cation, aromatic ring, and hydrophobic interactions.

Methods

Clinical Trial Identifier #NCT03238079



Study Outcome Measures

Primary Outcome Measure:

Demonstrate efficacy (mean annual acute serious bacterial infections (SBIs) is significantly less than 1/subject/year)

Secondary Outcome Measurements:

· Average serum IgG trough concentrations prior to each infusion
· Number of infection episodes (serious and non-serious)
· Number of days missed of work/school/daycare or,
· Number of days unable to perform normal daily activities due to infections
· Ability of the Investigational Medicinal Product to maintain stable, therapeutic IgG levels
· Episodes of fever
· Number of days of hospitalizations due to infections

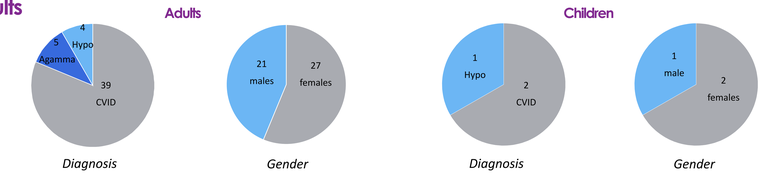
Dose for Adults

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

Dose for Children

	Age	Weight	Dose/Infusion
Average	9	37kg	535mg/kg
Range	4-17	25– 54kg	379-690mg/kg

Results



At the time of the last safety review (Nov 2018), 48 adult and 3 child subjects had been enrolled. The adults had been treated with PlasmaCap IG for a median of 162 (101-228) days. Six adult subjects withdrew between visits 3 and 6, three withdrew for reasons judged by the investigator to be unrelated to the product (n=3), the other three withdrew due to unrelated AEs; generalized pruritus (n=1), aseptic meningitis (n=1) and colon cancer (n=1).

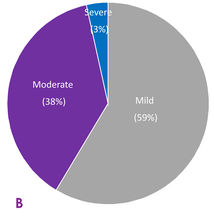
There were no Serious Bacterial Infections (SBIs) or study drug related Serious Adverse Events (SAEs).

96% of the 568 adult infusions and all of the 20 children's infusions to date completed without slowing, interrupting, or stopping.

All subjects (except one child*) completed all doses without the use of Pre-Medication. *The child who received pre-medication gradually eliminated pre-medication use completely by dose 4 to maintain the standard of care in his hospital.

A

Related AEs		
AEs	No. (%) of subjects (N=51)	
Severity		
Mild	17	(33%)
Moderate	11	(22%)
Severe	1	(2%)
Serious	0	(0%)
Type		
Headache	11	(22%)
Increased BP	2	(4%)
Fatigue	5	(10%)
Other	11	(22%)



B

Figure 5. As of the November 2018 safety review, the severity and type of drug related AEs (A) and the severity in relation to total drug related AEs (B).

Discussion

Although the data is preliminary and no statistical analysis can be done, the trend of adverse events per PlasmaCap IG infusion appears low (**Figure 5**). This, combined with the absence of study drug related SAEs after 52.4% of subjects completed their last dose and 28.5% of subjects completed their last visit suggests that PlasmaCap IG is safe and well tolerated. The low rate of adverse events per infusion may be a result of product purity or the process's ability to conserve high order structure of IgG. This is further highlighted by the fact that 96% of infusions to date were completed without slowing, interrupting or stopping the infusion.

Conclusions

The preliminary data of the ongoing clinical study appears 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.