

# **IGIV CLINICAL ENDPOINTS**

**Committee Update**

**Basil Golding, M.D., Chief  
Laboratory of Plasma Derivatives, Division of Hematology, OBRR, CBER, FDA**

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# Immune Globulin Intravenous (Human)

## Clinical Trial Proposal For Primary Immune Deficiency

Consensus: Clinical Review Branch, DH/OBRR  
Senior Management OBRR/CBER  
Statistician: Peter Lachenbruch Ph.D.

# Plasma Fractionation: Conclusions from BPAC Mar. 99

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- Multi-step process
- Variations can have far-reaching effects on safety and efficacy
- Each product should be regarded as unique and Immune Globulins should not be treated as a single generic biologic.

# Previous FDA Proposal: IGIV Trials (BPAC, Mar. 99)

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- A Prospective, Double-Blinded, Randomized, Phase III Study.
- Evaluation of efficacy and safety of new IGIV products in comparison to a licensed IGIV product.
- Sample size = 80 patients

# Problems with this Trial Design

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- Limited numbers of patients with PID that can be recruited for trials
- Multiple new IGIV Products to be tested
- Critical shortage of IGIV persists.

# New Proposal: Background

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- Discussion of possible trials that would reduce the sample size (internal, IDF)
  - PK studies
  - surrogate endpoints e.g. fever
- Justification for using historical controls
  - IGIV products have been very successful in limiting infections in PID patients
  - acute bacterial infections per patient per year =  $\geq 4$  without treatment, and  $\leq 0.5$  on treatment

# New Proposal: Study Design

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- Single-arm, 12 month, open study
- Compare to historical controls for safety, PK, and efficacy
  - 80% power
  - 99% confidence ( $\alpha = 0.01$ )
  - one-sided testing

# Clinical Trial Design: Safety

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Safety targets are based on previous trials.

- Historical control = 20% AERs per infusion
- target for trial to exclude > 40% AERs
- sample size ~ 40-50 patients receiving  $\geq 12$  infusions each

# Clinical Trial Design: Efficacy

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- Establish efficacy using an objective, clinically meaningful endpoint
  - primary endpoints: acute serious bacterial infections (pre-defined)
  - secondary endpoints: serum IgG levels, antibiotic treatment, hospitalizations, fever, etc.
- Sample size should be sufficient to determine whether the infection rate for the new IGIV is at or below the “beltline” ( $n \sim 40-50$ ).

# Clinical Trial Design: Efficacy (contd.)

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- Primary endpoint: acute serious bacterial infections
  - infections per patient per year  $\leq 0.5$  on approved IGIV
  - data with new product must exclude infection rate  $\geq 1$  infection per patient per year

# Clinical Trial Design: PK Studies

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- Washout period
- $C_{\max}$ ,  $T_{\max}$ , AUC, Cl, and T/2
- Trough levels
- Observed values should not be inferior to those concurrently or previously determined for approved products

# Clinical Trial: FDA Review

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- The trial would be considered a Phase III pivotal trial sufficient for licensure.
- Submissions with 6 month interim data can be submitted 6 months after the trial onset to initiate review of manufacturing, PK, and initial safety data.
- The efficacy and complete safety data will be submitted after termination, i.e each patient will be treated for 12 months.
- Initial FDA action is expected within 6 months of receipt of the completed data.

# Conclusions

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- Number of patients per trial will be reduced, permitting concurrent trials of new products.
- For approval, the new product will need to have acceptable safety, PK and efficacy profiles when compared to historical controls.
- Data will be collected during the trials to validate surrogate markers (e.g. antibodies against specific pathogens relevant to PID).