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A Phase I/IIa Trial of Intravenous Immunoglobulin Following Portoenterostomy in Biliary Atresia

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Abstract

Objectives.—Biliary atresia (BA) is a progressive neonatal fibroinflammatory cholangiopathy. We hypothesized that intravenous immunoglobulin (IVIg) would be safe, feasible, acceptable and efficacious for the treatment of BA. The primary objective of this study was to establish the feasibility, acceptability and safety profile of IVIg administration after hepatoportoenterostomy.

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(HPE) in BA. The secondary objective was to determine the treatment efficacy of IVIg based on good bile drainage and survival with the native liver.

**Methods.**—A multi-center, prospective, open-labeled, phase I/IIA trial of IVIg was conducted, with 1 gm/kg/dose of IVIg infused at 3-5 days, 30 days and 60 days post-HPE, and subjects followed for 360 days post-HPE. Twenty-nine participants completed the study.

**Results.**—Administration of IVIg infusions was feasible and acceptable in 79%. None of the serious adverse events (SAEs) were directly related to IVIg infusions, however 90% of participants had an SAE. Compared to a historical placebo-arm group, there was no significant increase in the proportion of IVIg participants with a serum total bilirubin < 1.5 mg/dL at 90, 180, or 360 days post-HPE. Survival with the native liver in the IVIg participants showed no significant benefit over the historical placebo-arm, with a difference at 360 days of −11.9% (IVIg:58.6%, placebo:70.5%; 90% UCB:2.1%; p>0.05).

**Conclusions.**—Although IVIg infusions in infants with BA post-HPE were feasible, acceptable and safe, there was no trend to lower bilirubin levels or improved 360 day survival with the native liver.

**Clinical Trial:** Safety Study of Intravenous Immunoglobulin Post-Portoenterostomy in Biliary Atresia; #NCT01854827.

Biliary atresia (BA) is a progressive fibroinflammatory cholangiopathy of infancy and the leading indication for liver transplantation in children. Hepatopportoenterostomy (HPE) is crucial to restoring bile drainage in infants with BA, but progression to end-stage liver disease still occurs in almost 80% of patients by age 20 years. Currently, no medical therapies improve the outcome following HPE; thus, there is a need to develop new treatments that would delay or prevent biliary cirrhosis in BA. A leading hypothesis regarding the pathogenesis of BA is that bile duct injury is initiated by a genetic variant, viral infection or toxin, followed by aggressive adaptive and innate immune responses targeting the bile duct epithelium, resulting in progressive fibrosis. Aberrant adaptive immune responses in BA consist of T cell and B cell activation, while innate immune responses include activation of macrophages, dendritic cells, and natural killer cells. Furthermore, deficits in regulatory T cells (Tregs) in BA allows for ongoing inflammation and biliary injury.

Intravenous immunoglobulin (IVIg) is used as immunotherapy for a variety of autoimmune and inflammatory disorders and has numerous mechanisms of action that result in suppression of adaptive and innate inflammatory-mediated injury. High dose IVIg regulates cellular immunity by inhibiting effector T cell functions and antigen presentation, neutralizing autoantibodies and promoting Treg capabilities. Indeed, many of the known IVIg targets of the immune system have been implicated as contributors to bile duct injury in BA. A decrease in the hepatic and biliary injury following high dose Ig administration in a virally-induced experimental mouse model of BA led us to hypothesize that IVIg might suppress the ongoing injury of the intrahepatic bile ducts in infants with BA, thus preventing or delaying the progression to biliary cirrhosis and improving outcomes. The aims of this study were to establish the feasibility, acceptability, tolerability, and safety profile of IVIg after HPE and to obtain preliminary efficacy data testing whether IVIg therapy was effective.
associated with improved bile drainage or improved survival without liver transplantation at 360 days after HPE.

PATIENTS AND METHODS

Study Design.

PRIME was a multicenter, single-arm, open-label Phase I/IIA trial of IVIg therapy following HPE in infants with BA conducted at 8 sites in the Childhood Liver Disease Research Network (ChiLDReN) funded by the NIDDK (clinicaltrials.gov NCT01854827). Ethical approval was obtained at each site; parents or legal guardians of the infants provided written informed consent. Enrollment was from October, 2013 through July, 2015 and a 360-day follow-up was completed July, 2016.

Patient Population.

Infants were recruited after the diagnosis of BA was established by intraoperative cholangiography, followed by performance of HPE and enrollment in the ChiLDReN prospective observational database study of cholestasis in infancy (PROBE; clinicaltrials.gov NCT00061828). Inclusion criteria were age ≤ 20 days, enrollment within 3 days of diagnosis of BA and HPE, serum direct or conjugated bilirubin level ≥ 2 mg/dL and ≥ 20% of total bilirubin, post-conception age ≥ 36 weeks, and weight ≥ 2000 g. Exclusion criteria included BA with extrahepatic congenital manifestations or another concurrent chronic condition prohibiting the use of IVIg (complete inclusion and exclusion criteria in Table, Supplemental Digital Content (SDC) 1).

To assess efficacy of IVIg administration and incidence of serious adverse events (SAE), we used placebo-treated participants from the ChiLDReN Steroids in BA Randomized Trial study (START) as a historical comparative group. Sixty four participants in START, conducted from 2005-2012 within the same institutions as the PRIME cohort, received placebo but were otherwise treated similarly to the PRIME participants (except for the IVIg intervention).

Study Intervention.

Participants received 3 infusions of 1 g/kg body weight of IVIg (Gamunex®-C, Grifols, Los Angeles, CA) over 4-8 hours at days 3-5, 30 and 60 days after HPE. Acetaminophen and diphenhydramine were administered before each infusion to reduce the risk of an infusion related AE. The first IVIg dose was given in the hospital post-HPE, while the last two doses could be given either on an out-patient basis or during a subsequent hospitalization. Routine clinical care guidelines for the postoperative care were established for infants enrolled in PROBE and were followed for all participants in this clinical trial; these included oral ursodeoxycholic acid (15-20 mg/kg/day) for 360 days after HPE, trimethoprim (TMP)-sulfamethoxasole (10 mg/kg/day TMP) for 180 days after HPE, high-MCT containing infant formula, and vitamin supplementation. Corticosteroid treatment was prohibited in PRIME. START placebo was administered orally for 13 weeks.
Measures.

Baseline assessments included the collection of demographic, medical, and surgical history; physical examination; laboratory parameters; and anthropometric measurements. The assessments were also performed at 14, 30, 60, 90, 180, 270 and 360 days after HPE. Serum IgG trough levels were measured at 60, 90, 180, 270 days post-HPE.

Study Outcomes.

Primary outcomes addressed the feasibility, acceptability and safety of IVIg. Feasibility was defined as the percentage of participants who received at least 80% of each of the three IVIg doses. Acceptability was defined as the percentage of participants for whom their family or caregiver allowed intravenous line placements, blood draws, and other study procedures. Safety and tolerability were assessed by three measures: the percentage of participants with any SAEs (defined as death, disability, life-threatening illness, or an event requiring or extending hospitalization), with any level 3, 4 or 5 toxicity (as defined per the NCI CTEP grading system), and with other expected adverse events (AEs) related to IVIg administration (allergic reactions, irritability, fluid volume problems, IV infiltration, and aseptic meningitis). Secondary outcome measures included efficacy (good bile drainage) and survival with native liver (SNL). Good bile drainage was defined as the percentage of participants with serum total bilirubin level of <1.5mg/dL with the native liver at 90, 180, and 360 days after HPE. SNL was defined as the time from HPE to liver transplantation or death (events), completed study follow-up (approximately 360 days after HPE) with native liver, withdrew, or was lost to follow-up (censored). Additional safety outcomes included time to first SAE, and the percentage of participants with infectious SAEs, unexpected AEs, and permanent discontinuation of IVIg owing to AEs. The list of a priori expected AEs appears in Table, SDC 2. An independent medical monitor and the DSMB reviewed all SAEs.

Statistical Analysis.

This Phase I/IIA study was primarily sized based on the precision to estimate the feasibility, tolerability and safety of IVIg in the population of infants with BA. With a sample size of 29 participants, with 20% loss-to-follow-up expected (resulting in 23 participants), we calculated there is 70%-79% power to detect a 40% or higher proportion of participants with an AE if the true proportion is 20% using a one-sided 10% Type I error rate and the exact one-sample binomial test. These considerations also apply to the other primary outcomes – feasibility, acceptability and tolerability. The power to compare preliminary efficacy (activity) outcomes between the IVIg participants and the historical controls from the START placebo group was also calculated. A one-sided testing strategy was chosen because of the interest in assessing whether IVIg resulted in unacceptable (high) safety parameters or improved the preliminary measures of efficacy (relative to historical placebo participants). There is 74%-82% power to detect a 50% relative (25% absolute) improvement in successful bile drainage with IVIg (assuming 51% good bile drainage at 360 days in the START placebo group) with a one-sided 10% Type I error rate and using the Fisher’s exact test for two proportions. Demographic and baseline laboratory characteristics were compared.
between the PRIME and START placebo participants using two-sample t-tests on the log scale for continuous outcomes and Chi-square tests for categorical outcomes.

The primary analysis was based on a modified intention-to-treat approach (mITT); all PRIME participants who received at least one dose of IVIg were included. A Per Protocol (PP) population was defined for sensitivity analyses and included all subjects in the mITT who received at least 2 of 3 IVIg doses, received adequate study medication exposure (>80% of any given IVIg dose) and who did not have a major protocol deviation. Fisher’s exact tests were used to compare the proportion of participants who had good bile drainage at each time point. Following liver transplant, a participant’s bilirubin levels were excluded from any subsequent analyses. Exploratory logistic regression analysis was performed with IVIg treatment (vs START placebo) and age at HPE as covariates. Odds ratios and one-sided 90% exact upper confidence bounds (UCB) were presented. The proportion of participants who survived with their native liver at 360 days after HPE was estimated among the IVIg treated participants and the START placebo controls by Kaplan-Meier methods. Descriptive statistics were summarized for serum total bilirubin values in PRIME and START placebo groups. For dichotomous safety outcomes, the proportion of participants experiencing the adverse outcome was summarized. Time to first SAE was summarized using Kaplan-Meier methods to estimate the SAE-free distribution. We examined whether the 60-day post-HPE serum trough IgG level impacted SNL using Cox proportional hazard models, adjusting for age at HPE. All analyses were performed using SAS version 9.3 (SAS Institute Inc.).

RESULTS

Study Population.

Fifty patients with BA were assessed for eligibility and the families of 30 participants consented to participate in PRIME (Figure 1). The mITT analysis set included 29 participants (97%) that had received their first dose of IVIg within 5 days of the HPE and had received either all 3 IVIg doses (N=25) or 2 doses (N=4). All 29 participants completed the study. The PP analysis set included 27 participants (90%), as one participant died after receiving a liver transplant within the study period and the other participant voluntarily withdrew from the study (protocol deviation). The historical comparative group that met the PRIME eligibility criteria consisted of 64 of the 70 START placebo participants.

Demographic and baseline characteristics were comparable between the two groups, including the mean age at HPE (60±19 [mean ± SD] PRIME IVIg vs. 67±22 days, START placebo), gender, race, and ethnicity (Table 1; Table, SDC 3). Baseline laboratory tests were similarly abnormal in both groups, including serum total bilirubin (8.3±3.4 mg/dL PRIME vs. 7.8±2.8 mg/dL START placebo) and conjugated/direct bilirubin (4.5±1.6 vs. 5.0±2.0 mg/dL). Statistically significant, but not clinically significant differences, were observed in alkaline phosphatase (489.3±203.89 U/L PRIME vs. 634.3±271.08 START placebo; p=0.01) and hemoglobin (11.5±2.11 g/dL vs 10.4±1.29 g/dL; p=0.004). Biochemical indicators of hepatobiliary injury and synthetic function were similar in both groups (Table 1).

Measurement of serum IgG showed that PRIME participants had above the upper limit of normal at time points 60, 90 and 180 days after HPE (day 60: 814±247 mg/dL; day 90: 814±247 mg/dL; day 180: 814±247 mg/dL).
926±227 mg/dL; day 180: 783±469 mg/dL). Normal mean levels of serum IgG for age were detected at subsequent time points (day 270: 642±391 mg/dL; day 360: 824±485 mg/dL). There was no statistically significant evidence of association of serum IgG level at day 60 and subsequent good bile drainage at 90, 180 or 360 day time points based on Cox proportional hazard models adjusting for age at HPE (data not shown).

**Primary Endpoints.**

A summary of all primary outcomes is provided in Table 2. In the mITT analysis, the administration of > 80% of all three IVIg infusions was feasible in 23 of 29 participants (79%; 90% lower confidence bound 63.2%) and was acceptable to the families of 23 participants (79%; 90% lower confidence bound 63.2%). Reasons for the lack of feasibility or acceptance of the administration of infusions included difficulty attaining or maintaining the IV (N=2), inability to get to the infusion center due to transportation issues (N=1), caretaker request to not administer the infusion (N=2), lack of administration of full dose (<80% of total; N=1) and the need to list for liver transplant (N=1). There may have been more than one reason for lack of feasibility/acceptance for a given participant.

There were no SAEs related to the IVIg infusions. Eight participants (28%; 14.5% lower confidence bound) had other expected AEs related to the IVIg infusions [irritability (N=1), hypertension (N=4), hypotension (N=1), fever (N=1), other (N=1)], however none required termination of an infusion. Twenty six PRIME participants (90%; 75.4% lower confidence bound) had an SAE prior to liver transplant during the study and 26 had level 3, 4, or 5 toxicity. Time to first SAE during the study period (Figure, SDC 4) showed that approximately 50% of participants had experienced an SAE by 60 days. Prior to liver transplantation, 26 of 29 PRIME participants (90%) experienced 83 SAEs (an average of 2.9 per participant) compared to 48 of 64 START placebo participants (75%) who experienced 134 SAEs (an average of 2.1 per participant) over the same time period (Tables, SDC 5,6,7). The most common SAEs reported included cholangitis, fever/ virus infection, malnutrition and ascites (Table, SDC 5). One death occurred in PRIME on post-operative day 1 of liver transplantation, due to intraabdominal bleeding and hemodynamic compromise.

**Secondary Endpoints.**

Compared to the START placebo group, there was no significant increase in the proportion of PRIME participants that met the secondary endpoints of serum total bilirubin < 1.5 mg/dL with their native liver at 90, 180, or 360 days after HPE. Adjusting for age at HPE, the adjusted odds ratio at 90 days was 0.67 (2.38; 90% upper confidence bound), at 180 days 0.33 (1.22), and at 360 days 0.29 (1.24), none of which reached statistical significance (Figure 2A). Sensitivity analyses support the conclusions of this primary analysis. In a PP analysis including 27 PRIME participants, the percent of participants with a total serum bilirubin < 1.5 mg/dL at each time point was similar to the mITT analysis, achieving no signal of a benefit of IVIg when compared to the START placebo group. Furthermore, serum total bilirubin levels at each time point were similar between the PRIME IVIg and the START placebo groups (Figure 2B). The number of children transplanted during the 360 day follow-up period was 12/ 29 (41.4%) in the PRIME IVIg group and 17/ 57 (29.8%) in the START placebo group. Within the PRIME IVIg group, there was no significant difference in
incidence of liver transplant between those children who had HPE performed at ≤60 days of age (5 of 14 participants) compared to those with HPE performed after 60 days of age (7 of 15 participants) (p=0.72 Kaplan-Meier analysis). Survival with native liver in the PRIME participants showed no significant benefit over that of the START placebo group, with a difference at 360 days of −11.9% (PRIME IVIg 58.6%, START placebo 70.5%; 90% upper confidence bound: 2.1%; p>0.05) (Figure 2C).

DISCUSSION

A leading etiologic theory of BA is that of a progressive, immune-mediated inflammation targeting the bile duct epithelium, with excessive activation of both adaptive and innate immune responses. To that end, we sought to determine if the immunomodulatory properties of IVIg were sufficient to inhibit the biliary inflammation in BA. The results show that the therapy was both feasible and acceptable in 79% of participants enrolled. This study tested IVIg use in infants with BA, whose very nature would be expected to result in many SAEs, as observed in nearly 90% of PRIME participants. However, none of the SAEs or instances of liver test abnormalities were ascribed to the IVIg itself. Overall, the per-protocol use of IVIg in the setting of infants with BA can be considered safe and tolerable.

The efficacy hypothesis tested in the study was that IVIg would improve bile drainage outcome of BA after HPE. Since the use and safety of IVIg had never been reported in BA patients, a randomized, placebo-controlled trial could not be justified at this stage of testing of IVIg. Thus, we elected to compare IVIg treated participants in PRIME to similar participants in the placebo arm of the START trial, utilizing the same sites for both studies. The PRIME study had sufficient power to identify a 50% relative (25% absolute) improvement in bile drainage outcome compared to START placebo patients. The results of this comparison show that treatment with IVIg does not show a signal towards improved outcome. The one-way test of efficacy design of the study precluded our ability to determine if IVIg therapy would result in worse outcomes than no therapy. We noted, however, that 41% of START placebo participants had a good outcome at 360 days and, unexpectedly, only 24% of PRIME participants had good outcome. The reasons for this trend towards a worse outcome in relation to IVIg administration are not clear as the vast majority of mechanisms of action of IVIg are generally strongly anti-inflammatory. A few exceptions to this include IVIg-induced upregulation of co-stimulatory molecules on antigen presenting cells (B7-1, B7-2, CD40) and increased dendritic cell production of IL-33. Interestingly, IL-33 is upregulated in a subset of BA patients and stimulates Th2 cell activation and bile duct proliferation. IL-33 also has pro-fibrotic effects related to the expansion of liver resident innate lymphoid cells.

Limitations of using historical controls include biased estimates of treatment differences and either reduced power or increased type I error (depending on the direction of the bias) if the historical data are not sufficiently comparable to the experimental (IVIg) arm. In the IVIg trial, some of the potential limitations were mitigated by using the same network of sites, comparable patient populations and equivalent definitions of the efficacy (secondary) end points. Another limitation is that data were not collected on patients who were approached for the PROBE study but declined PRIME enrollment. Thus we could not ascertain whether
there was any selection bias of those enrolled in PROBE. Finally, this study was performed based on the hypothesis that the bile duct injury in BA is a consequence of an aberrant immune response. Other theories on the etiology of BA include toxin induced, genetic mutation associated with biliary development or ischemia of the liver; etiologies that would not be predicted to respond to immunosuppression.\textsuperscript{42} Furthermore, there is evidence that the biliary injury is occurring prior to birth, based on elevated direct bilirubin levels at the time of birth. It is plausible that significant biliary damage and fibrosis occurring in-utero would not be reversible post-HPE with any treatment.\textsuperscript{43}

In conclusion, IVIg in infants with BA post-HPE was feasible, acceptable and safe. However, despite this study not being powered to detect efficacy or harm, the lack of a trend to improvement in bilirubin levels and the unexpectedly low 360-day survival with the native liver reduces enthusiasm for a larger clinical trial of IVIg in BA.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**Abbreviations:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>BA</td>
<td>biliary atresia</td>
</tr>
<tr>
<td>ChiLDReN</td>
<td>Childhood Liver Disease Research Network</td>
</tr>
<tr>
<td>HPE</td>
<td>hepatopancreatoduodenal reconstruction</td>
</tr>
<tr>
<td>IVIg</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>mITT</td>
<td>modified intention to treat</td>
</tr>
<tr>
<td>PP</td>
<td>per protocol</td>
</tr>
<tr>
<td>PRIME</td>
<td>Phase I/IIa Trial of Intravenous Immunoglobulin Therapy Following Portoenterostomy in Infants with Biliary Atresia</td>
</tr>
<tr>
<td>PROBE</td>
<td>Prospective Observational Database Study of Cholestasis in Infancy</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>START</td>
<td>Steroids in Biliary Atresia Randomized Trial</td>
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</table>
Tregs  regulatory T cells

References.


What is Known.

- Biliary atresia is an inflammatory fibrosing cholangiopathy for which there is no treatment post-portoenterostomy that delays progression of disease.

What is New.

- Intravenous immunoglobulin therapy was safe, feasible and acceptable, however it did not change the outcome of the disease and is not recommended as a potential therapy for biliary atresia.
Figure 1.
CONSORT Flow Diagram. Details on participant enrollment, treatment, follow-up, and data analysis are provided.
Figure 2.
Secondary Outcomes. 
A. Percent with good bile drainage post-hepatoportoenterostomy (HPE) (total bilirubin < 1.5 mg/dL).
B. Total bilirubin prior to liver transplantation [median (dash), interquartile range (box), 1.5*IQR (whiskers), outliers >1.5*IQR (circles), grey line: bilirubin level of 1.5 mg/dL].
C. Kaplan-Meier analysis of the proportion of participants with survival with the native liver (SNL) and the time from HPE to liver transplantation or death (p>0.05).
Table 1.
Demographic Characteristics and Baseline \(^{1}/\) Laboratory Tests by Treatment Group (mITT Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRIME IVIg Participants (N=29)</th>
<th>START Placebo Participants (N=64)</th>
<th>P-value (^{4}/)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Female, N (%)</td>
<td>18 (62%)</td>
<td>37 (58%)</td>
<td>0.6989</td>
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<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td>0.1097</td>
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<tr>
<td>White/ Caucasian</td>
<td>22 (76%)</td>
<td>42 (66%)</td>
<td></td>
</tr>
<tr>
<td>Black/ African American</td>
<td>3 (10%)</td>
<td>9 (14%)</td>
<td></td>
</tr>
<tr>
<td>Other (^{2}/)</td>
<td>4 (14%)</td>
<td>13 (21%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
<td>0.8651</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (31%)</td>
<td>21 (33%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>20 (69%)</td>
<td>43 (67%)</td>
<td></td>
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<tr>
<td>Age at HPE, days (mean±SD)</td>
<td>60.0±18.6</td>
<td>67.1±22.2</td>
<td>0.1379</td>
</tr>
<tr>
<td>Age at HPE, N (%)</td>
<td></td>
<td></td>
<td>0.2216</td>
</tr>
<tr>
<td>≤ 30 days</td>
<td>2 (7%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30 to ≤ 45 days</td>
<td>5 (17%)</td>
<td>8 (13%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 45 to ≤ 60 days</td>
<td>7 (24%)</td>
<td>18 (28%)</td>
<td></td>
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<tr>
<td>&gt; 60 to ≤ 90 days</td>
<td>14 (48%)</td>
<td>26 (41%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 90 to ≤ 120 days</td>
<td>1 (3%)</td>
<td>11 (17%)</td>
<td></td>
</tr>
<tr>
<td>Serum laboratory tests at baseline (mean±SD)</td>
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<td></td>
<td></td>
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<tr>
<td>Total bilirubin, mg/dL</td>
<td>8.3±3.4</td>
<td>7.8±2.8</td>
<td>0.5358</td>
</tr>
<tr>
<td>Direct/ conjugated bilirubin (^{3}/), mg/dL</td>
<td>4.5±1.6</td>
<td>5±2.0</td>
<td>0.2550</td>
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<td>GGTP, U/L</td>
<td>654.8±479.0</td>
<td>729.8±573.9</td>
<td>0.5548</td>
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<tr>
<td>ALT, U/L</td>
<td>161.8±104.4</td>
<td>179.8±131.1</td>
<td>0.6510</td>
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<tr>
<td>AST, U/L</td>
<td>214.0±108.2</td>
<td>235.1±121.4</td>
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<td>INR</td>
<td>1.1±0.3</td>
<td>1.1±0.4</td>
<td>0.6142</td>
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<tr>
<td>Albumin, g/dL</td>
<td>3.6±0.5</td>
<td>3.6±0.5</td>
<td>0.5886</td>
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<td>Platelets, × 10(^{3}/) mm(^{3})</td>
<td>442.8±122.4</td>
<td>441.5±151.0</td>
<td>0.7616</td>
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</tbody>
</table>

\(^{1}/\) Baseline is defined as the time period prior to HPE

\(^{2}/\) Other: Asian, American Indian, Alaskan Native, other, not reported

\(^{3}/\) Either direct or conjugated bilirubin values are summarized, with direct being used if both values are reported

\(^{4}/\) Two-Sample T-Test for Continuous Data; Chi-Square Test for Categorical Data
### Table 2.

Summary of Primary Outcomes (mITT Analysis)

<table>
<thead>
<tr>
<th>Variable/Statistic</th>
<th>PRIME Participants (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility [^1], N (%)</td>
<td>23 (79.3%)</td>
</tr>
<tr>
<td>90% Lower Confidence Bound [^2]</td>
<td>63.2%</td>
</tr>
<tr>
<td>Acceptability [^3], N (%)</td>
<td>23 (79.3%)</td>
</tr>
<tr>
<td>90% Lower Confidence Bound [^2]</td>
<td>63.2%</td>
</tr>
<tr>
<td>Safety and Tolerability</td>
<td></td>
</tr>
<tr>
<td>Participants with any serious adverse events [^4], N (%)</td>
<td>26 (89.7%)</td>
</tr>
<tr>
<td>90% Lower Confidence Bound [^2]</td>
<td>75.4%</td>
</tr>
<tr>
<td>Participants with level 3,4 or 5 toxicity (per NCI CTEP grading system), N (%)</td>
<td>26 (89.7%)</td>
</tr>
<tr>
<td>90% Lower Confidence Bound [^2]</td>
<td>75.4%</td>
</tr>
<tr>
<td>Participants with other expected adverse events [^5]</td>
<td>8 (27.6%)</td>
</tr>
<tr>
<td>90% Lower Confidence Bound [^2]</td>
<td>14.5%</td>
</tr>
</tbody>
</table>

\[^1\]% of participants for whom administration of IVIg was feasible, defined as the successful administration (at least 80% of each dose) of the 3 doses of IVIg at the prescribed times

\[^2\]One-sided 90% Clopper-Pearson lower confidence bound

\[^3\]% of participants for whom the study was acceptable, defined as the ability of the family or guardian to allow intravenous line placement, blood draws and other study procedures

\[^4\]% of participants with SAEs prior to liver transplantation

\[^5\]Expected adverse events were defined as common side effects attributable to the use of IVIg