Utilization of Funded Multi-center Prospective Longitudinal Databases to Inform Clinical Trials in Rare Diseases – Examination of Cholestatic Liver Disease in Alagille Syndrome

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Abbreviations

ALGS = Alagille syndrome

ALGS NH = Alagille Syndrome Natural History

ALT = alanine aminotransferase

ASBTi = acid transport inhibitors

AST = aspartate aminotransferase

ChiLDReN = Childhood Liver Disease Research Network

CI = confidence intervals

CSS = clinician scratch scale

IBATi = ileal bile acid transport inhibitors

IRB = Institutional Review Board

LOGIC = Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases

SD = standard deviation

SE = standard error

SMD = standardized mean difference

SIEHC = Surgical interruption of the enterohepatic circulation

TB = total bilirubin

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Abstract

The conduct of long-term conventional randomized clinical trials in rare diseases is very difficult, making evidenced-based drug development problematic. As a result, real world data/evidence are being more frequently utilized to assess new therapeutic approaches in orphan diseases. In this novel investigation, inclusion and exclusion criteria from a published trial of maralixibat in Alagille syndrome (ALGS, ITCH NCT02057692) were applied to a prospective longitudinal cohort of children with cholestasis (LOGIC NCT00571272) to derive contextual comparator data for evolving clinical trials of intestinal bile acid transport inhibitors in ALGS. A natural history/clinical care cohort of 59 participants who met adapted inclusion and exclusion criteria of ITCH was identified from 252 LOGIC participants with ALGS with their native liver. Frequency weighting was utilized to match the age distribution of ITCH and yielded a cohort (ALGS NH) that was very similar to the baseline status of ITCH participants. During a two year prospective follow-up there was a significant reduction in pruritus in the weighted ALGS NH cohort as assessed by the clinician scratch score (-1.43 [0.28] -1.99,-0.87; mean[SE] 95% CLM). During the same time period total bilirubin, albumin and alanine aminotransferase (ALT) levels were unchanged, while platelet count dropped significantly (-65.2 [16.2] -98.3,-32.1). Weighted survival with native liver was 91% at two years in the ALGS NH. These investigations provide valuable real-world data which can serve as contextual comparators to current clinical trials, especially those without control populations, and highlight the value and importance of funded multi-center prospective natural history studies.

Despite focused interest and investment of significant resources there remains an unmet need in developing proven therapeutic approaches to clinical issues related to rare diseases (1-3). Conventional randomized controlled trials often are not feasible due to a variety of issues, most notably the lack of statistical power due to inadequate numbers of potential study participants. Complex ethical issues arise in development of clinical trials in light of the lack of evidenced-based approaches to therapy for rare diseases. Conventional clinical trial design often necessitates inclusion of a placebo arm, which may not be tenable for individuals and families burdened with poorly understood disorders and debilitating symptoms. This is particularly problematic for severe potentially life-threatening diseases, where the studied intervention requires a prolonged course of therapy to demonstrate efficacy.

Alagille syndrome (ALGS) is a rare systemic genetic disorder with a complex clinical phenotype that is not readily predicted on the basis of genotype or family history (4). One of the major and debilitating manifestations of ALGS is pruritus related to cholestasis, which has a pronounced impact on sleep and quality of life for patients and their families (5). Until very recently, available pharmacologic therapies had limited efficacy in ameliorating itch, leading to the need for invasive surgical interventions including surgical interruption of the enterohepatic circulation (SIEHC) and/or liver transplantation (6). In this context there has been ongoing work seeking to identify novel pharmacologic therapies for pruritus in ALGS. One candidate approach is the use of inhibitors of intestinal bile acid reclamation (ileal bile acid transport inhibitors, IBATi, also known as apical sodium dependent bile acid transport inhibitors, ASBTi) as a surrogate for SIEHC (7, 8). Two of these agents have recently been approved by the Food and Drug Administration for the treatment of cholestatic pruritus, odevixibat for progressive familial intrahepatic cholestasis and maralixibat for ALGS. The time course of maximal response to SIEHC is not well delineated and may be weeks, months or years. Coincident with this response to SIEHC is a potential for slow improvement in pruritus in ALGS as part of its “natural history” (9).

In the context of this complex clinical problem, investigational trials of IBATi as a potential treatment for pruritus in ALGS have been undertaken (10). Short-term randomized placebo controlled trials have been completed and have demonstrated potential therapeutic efficacy (11). An alternative study design has used a randomized placebo controlled temporary withdrawal of therapy as a marker of efficacy (ICONIC NCT02160782) (12). These studies are complicated by significant potential placebo and nocebo effects, which are common in trials of agents directed at the treatment of pruritus (13). There is a critical need to determine the long-term potential efficacy of these agents, but prolonged treatment with placebo is likely not to be acceptable to patients and their families, investigators, clinicians and potentially regulatory agencies.

The current investigation sought to determine the feasibility of assessing the outcome of a natural history cohort derived from a prospective longitudinal clinical database study focused in part on ALGS that could potentially serve as a control arm for a single arm clinical trial. The Childhood Liver Disease Research Network (ChiLDReN) is a multi-center consortium based primarily in the United States, which is funded by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK). The Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis (LOGIC – NCT00571272) has been conducted by ChiLDReN since 2007 and has enrolled over 300 participants with ALGS (9). The current study sought to utilize the entry criteria for one of the IBATi ALGS clinical trials (ITCH NCT02057692, [11]) to identify a natural history cohort that might be used as a control population for existing clinical trials for ALGS. This approach addresses the United States Food & Drug Administration's Real World Evidence Program [https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence](14, 15).

Experimental Procedures

The inclusion and exclusion criteria for ITCH were adapted to information available in the prospective longitudinal database, LOGIC (Table 1) (9, 11). LOGIC participants with ALGS were enrolled between November 1, 2007 and December 31, 2019. Eligibility for ITCH utilized a novel investigational measure of caregiver reported pruritus manifestations, ItchRO, and was dependent upon an average ItchRO score of $\geq$2 assessed daily during a two-week screening period (11, 16). This measure was not available in routine clinical practice and as such the clinician scratch scale (CSS) developed by Whitington was used in its place (17). Although CSS was an outcome measure in ITCH, it must be acknowledged that CSS and ItchRO do not appear to correlate (18). The composition of the cohort for this analysis was finalized prior to the performance of any outcome assessments for the cohort. Besides applying the inclusion and exclusion criteria of ITCH, eligibility for this study necessitated the potential for at least one follow-up visit after enrollment in LOGIC, which served as the baseline. Per the LOGIC protocol follow-up was scheduled on an annual basis with collection of clinical and laboratory data derived as part of routine clinical care. PedsQL was obtained in participants as logistically possible as a part of the LOGIC research protocol. Participants remained eligible for analysis if their only follow-up after the baseline visit was for liver transplant or death as these were sentinel events collected in LOGIC. Participants who were otherwise lost to follow-up after the baseline enrollment visit with no intervening follow-up visits were excluded from the analysis. Prior to calculating changes at one and two year follow-up, clinically relevant changes in key parameters were defined based upon investigator consensus (Supplemental Table 1).

The resulting cohort was different from the ITCH cohort with regard to some baseline characteristics, especially in terms of a disproportionate number of participants < 2 years of age (Table 2) compared to the ITCH cohort. Since individual-level data of the baseline ITCH cohort were not available, it was not possible to use the commonly used method, propensity score inverse probability weighting, to adjust for difference between the two cohorts. Therefore a

weighting approach was utilized to calibrate the age distribution of the ALGS natural history cohort to the age distribution of the ITCH/IMAGINE II cohort. Unweighted and weighted means, medians, or proportions of baseline characteristics in the Alagille Syndrome Natural History (ALGS NH) cohort were calculated. To compare the unweighted and weighted summary statistics of the ALGS NH cohort to the ITCH/IMAGINE II cohort, standardized mean difference (SMD) for all continuous variables at baseline were calculated. A sensitivity analysis was performed using the last value carried forward for participants who died or underwent liver transplant. Chi-square test or Fisher's exact test were used for comparing unweighted distribution of categorical variables in the ALGS NH cohort to their distribution in the ITCH/IMAGINE II cohort. Wald Chi-square tests were used to compare weighted distributions of categorical variables in the ALGS NH cohort to their distribution in the ITCH/IMAGINE II cohort. Taylor series method was used to calculate standard deviation (SD), standard error (SE), and 95% confidence intervals (CI) for weighted means and medians, and Kaplan-Meier estimates of transplant free survival over time.

Results

Cohort Derivation

Between November 1, 2007 and December 31, 2019 1,261 participants were enrolled in LOGIC. Of these, 1,009 were excluded: 856 had a diagnosis other than ALGS, 89 were enrolled after liver transplant, three were enrolled as siblings without liver disease (for genetic investigations), 27 did not meet the age criteria for the study and 34 had no follow-up information. The inclusion and exclusion criteria were then applied to the remaining 252 participants in LOGIC who had ALGS. The criteria to define cholestasis, as shown in Figure 1, were applied resulting in 53 participants excluded for absent evidence of this definition of cholestasis. Exclusion criteria were then applied to the remaining 199 participants leading to the identification of 59 LOGIC participants with ALGS who met the ITCH-derived inclusion and exclusion criteria.

Baseline parameters for the cohort of 59 LOGIC ALGS participants are shown in Table 2 and compared to the baseline characteristics of the published cohort of ITCH participants (11). The percentage of LOGIC ALGS participants whose baseline visit was at age < 2 years was disproportionately high in the original cohort; frequency weighting was applied to correct for this important discrepancy. In general, the weighted LOGIC ALGS NH cohort was well-matched to the baseline characteristics of the ITCH cohort. PedsQL parent total score was higher in the weighted ALGS NH cohort. LOGIC participants were eligible to enroll in ITCH and it is worthwhile noting that 17 LOGIC participants with ALGS were excluded from this cohort due to participation in a drug trial, which was likely ITCH. Serum bile acids and albumin levels were lower in the weighted ALGS NH, although bile acids were measured in only 14 ALGS NH participants and the difference in mean albumin levels was only 0.3 mg/dL.

Change in Key Clinical Parameters at One and Two Year Follow-up

Weighted mean values for key clinical parameters (CSS, total bilirubin (TB), ALT, platelet count, albumin, weight and height) at baseline, year one and two of follow-up are shown in Supplemental Table 2. Change from baseline for these parameters is shown in Table 3. Similar results were found when the last value measured was carried forward as a sensitivity analysis for the impact of death or transplant in the first two years of follow-up (Supplemental Table 3). There was a significant reduction in CSS at years one and two of follow-up (Figures 2A-2B).

Nine of 40 participants evaluated at two years had complete resolution of their baseline pruritus as assessed by CSS (Figure 2B). Platelet count was reduced at year two of follow-up. Height z-score was increased at one and two years of follow-up. No changes were observed for TB, ALT, albumin, or weight. The statistically significant changes from baseline for CSS and platelet count were reflected in the percentages of participants with clinically relevant changes in the same parameters (Supplemental Table 4). By year two, 73% had a clinically relevant reduction in CSS and 58% had a clinically relevant reduction in platelet count. One third of the participants had a clinically relevant increase in height and weight z-score at two years of follow-up. The percentage of participants receiving various commonly used medications for the treatment of pruritus was stable during the two years of follow-up (Supplemental Table 5).

Sentinel Events

The occurrence of sentinel events was tracked during the available follow-up for the ALGS NH cohort of 59 participants. The duration of observed follow-up for this cohort ranged from four months to 12 years with an average of five years. During that time period, three participants developed clinically evident ascites (at ages 3, 12 and 23 years), none had variceal hemorrhage and three underwent surgical interruption of the enterohepatic circulation (one had partial biliary diversion, one had ileal exclusion, one underwent both procedures; partial biliary diversion followed 1.5 years later by ileal exclusion). SIEHC took place between the baseline and the year-1 visit in the three cases where surgery was undertaken. After SIEHC and within two years of baseline there was no change in CSS in one and reductions of CSS by one and two in the other

two. Three children died with their native liver during follow-up at an average age of 3.5 years. Thirteen children underwent liver transplant at a mean age of 5.3 years. Of those who died or underwent liver transplant during follow-up, nine were under two years of age, six were two to three and only one was three or older at enrollment. Survival with native liver is shown in Figure 3A. Given the preponderance of young children who did not survive with their native liver, a weighted survival curve is shown in Figure 3B and reveals 91% survival with native liver two years from baseline.

Discussion

These investigations demonstrate the feasibility and potential utility of using funded multi-center prospective clinical registries as contextual comparators for clinical trials in rare diseases. The approach meets the mandate of the CURES Act to accelerate medical intervention by using Real World Data and Evidence in the context of guidance from the Food and Drug Administration. In this circumstance, the cohort was relatively contemporaneous to the model clinical trial in question (11), thereby enhancing its utility. In addition, the application of inclusion/exclusion criteria increased the relevance of the data set. This clinical care/natural history cohort was derived from a large-scale NIDDK funded effort that was conducted over a period of greater than ten years and encompassed investigations in more than 15 academic centers with clinical expertise in pediatric hepatology. Access to data from 5-fold more participants than were selected as a comparator was required. This kind of an effort almost certainly necessitates significant funding. The information found within the LOGIC database was generally robust enough for a fairly accurate application of the inclusion and exclusion criteria of ITCH. The definition of ALGS was well established and the collaborative development of ITCH by ChiLDReN and Lumena/Shire/Takeda/Mirum through a Cooperative Research and Development Agreement enhanced the concordance of the ALGS definition. The ITCH protocol specified a number of parameters that were collected as part of the operation of the clinical trial. The LOGIC protocol specified collection of clinical information that was obtained primarily as part of clinical care. This resulted in some discrepancies the most significant of which is the baseline criteria for pruritus, which is addressed below. Enrollment in ITCH necessitated an assessment by the local investigator that the potential participant would be able to complete the 13 week trial. This was difficult to apply to the LOGIC database and listing for liver transplant was used as a surrogate for advanced liver disease that might preclude completion of the clinical trial. The other factor that could not be accurately assessed within LOGIC was the severity of cardiac disease, which can be significant in ALGS (19). A number of historical clinical issues were queried in ITCH, which were not recorded in the LOGIC database including as examples, chronic diarrhea requiring intravenous fluids, history of encephalopathy,

and concerns for nonadherence. Serum bile acid levels and fat soluble vitamin sufficiency were used in ITCH entry criteria, but were sporadically available in the clinical care of LOGIC participants.

As noted above one of the key issues in the application of the ITCH entry criteria to the LOGIC cohort was the assessment of pruritus severity. Quantitative assessment of pruritus remains an elusive goal in hepatology (18). In the ITCH trial a novel tool, ItchRO, was developed to quantify caregiver and/or patient report of features of pruritus that were most relevant as determined by qualitative interviews and formal instrument development (16). Key questions in ItchRO relate to observed scratching, skin manifestations of scratching, and sleep disturbance. This instrument is not in use in routine clinical care and was not available within LOGIC. ItchRO was used not only as an entry criterion but as a major end-point of the randomized placebo- controlled trial of maralixibat (11). The entry criteria for ITCH relied upon twice daily assessment of pruritus as measured by ItchRO for two weeks. The CSS, a very different assessment of pruritus which is used in clinical care of children with cholestasis, was collected in LOGIC (17). This assessment of pruritus relies upon clinical observation of scratching behavior and/or skin manifestations of scratching during a clinical encounter. CSS was collected in ITCH. Clearly these are different assessments of pruritus and it is not entirely unexpected that the two measures do not correlate with each other (18). In ITCH both ItchRO and CSS were reduced in participants who received maralixibat compared to those that received placebo. As such, CSS was felt to be a reasonable although not equivalent parameter for this analysis.

The comparator cohort from LOGIC had many essential similarities at baseline compared to the ITCH cohort. A major and critical difference however was the age distribution, with a very disproportionate number of young participants in the LOGIC cohort. This was felt to be a crucial difference that could impact on outcomes. Very young children with ALGS and cholestasis are more predisposed to worse outcomes and a need for early transplantation, particularly for intractable pruritus (20). In light of this potential confounder a weighting method was used to

match age distribution at enrollment between the ITCH and LOGIC cohorts. The decision to use this weighting method was arrived at before any outcome measures were assessed. The weighted ALGS NH cohort was very similar to the ITCH cohort.

Notable differences, however, were serum bile acid and albumin levels along with PedsQL. While statistically significant, the clinical significance of the differences in bile acids and albumin are unclear. Bile acids are not routinely measured in the clinical practice of many and as such only 14 LOGIC participants had this important parameter assessed. Serum albumin was lower in the weighted cohort, which could be interpreted as being consistent with more severe disease, although the values do not really support the conclusion. The findings in PedsQL are potentially important, although this important assessment was only conducted in 21 of the participants in the weighted cohort. PedsQL was the parental total score and was significantly lower in the ITCH cohort. Parental perception of poor quality of life may have been an incentive to enroll in ITCH and as such may have led to the observed discrepancy.

The data derived from this kind of analysis can be quite useful to put the results of clinical trials in context, but should not be used for direct comparisons to distinct clinical trials. The outcomes focused on in this investigation were ones that were commonly assessed in routine clinical practice and ones that were amenable to an empiric *a priori* assignation of clinical relevance. One of the major findings was that pruritus as measured by CSS improved significantly in the two years of clinical follow up in LOGIC. There was not an easily identifiable change in clinical practice that would explain this change. It has been surmised by many that pruritus improves over time in ALGS. One could also hypothesize a potential bias of clinicians to support the value of their clinical practice by identifying an improvement in one of the major manifestations of the disease that they are treating in their patients. As CSS is clinician scored, this potential bias could have impacted the change over time in this parameter. An additional important parameter that changed over time was platelet count, which fell significantly after two years of follow-up. This is not unexpected as progressive fibrosis and portal hypertension in cholestatic liver disease could lead

to increased hypersplenism and a commensurate reduction in platelet count. While statistically significant, the increase in height z-score in this study is of uncertain clinical significance. The contextual meaning of these findings may be apparent from review of experiences with the use of maralixibat over the long-term in ALGS. In the combined experiences of several recent trials IMAGO(NCT 01903460)/ITCH (NCT 02057692)/IMAGINE (NCT 02047318)/IMAGINE II (NCT 02117713) and also the ICONIC trial (NCT 02160782), there was also the observation of a significant improvement of pruritus over one to two years of treatment with maralixibat (21). Platelet count was also observed to decrease in these clinical trials. One notable difference, of uncertain significance, was the increase in ALT observed in these clinical trials, which was not seen in this natural history cohort.

Ultimately, one strives to identify approaches that will alter the natural history of ALGS and other rare diseases. Often this requires the assessment of endpoints that are comprised of sentinel events, in the case of liver disease markers of hepatic decompensation, perceived need for liver transplant or death. This analysis provides critical information about progression to these important endpoints during clinical practice that avails currently available therapies. In this cohort the development of sentinel events was relatively infrequent. Interestingly there were no episodes of variceal hemorrhage and only three individuals developed ascites. Many more underwent liver transplantation, which suggests that it may have been for intractable and incapacitating pruritus. Survival with native liver at two and four years was 91% and 87% in the weighted cohort. An intervention would need to be extremely efficacious to yield a significant improvement in this survival in the setting of the relatively small numbers of individuals affected by this rare disorder who might be eligible for a conventional randomized clinical trial. It is noteworthy that the Food and Drug Administration approval of odexivibat and maralixibat were for impact on pruritus not changes in long-term disease progression.

In summary, the current studies have shown that prospective longitudinal database registries can be utilized to provide important and unique contextual information regarding interventional clinical

trials in rare diseases, especially in those that are single arm studies or lack a control population. Application of inclusion and exclusion criteria to a robust registry provides information that is potentially more precise and relevant than broadly constructed real-world natural history data. The findings from this kind of real-world evidence are critically important given the difficulties of conducting long-term placebo controlled trials in orphan diseases. There are potential limitations on application of entry, inclusion and exclusion criteria related to the scope of data collected in routine clinical practice relative to a formal clinical trial. With adequate numbers of participants in a registry, relevant matching to important clinical features is feasible. Caution should be exercised in the comparisons of the data derived from these observational databases with interventional trials. Formal statistical comparisons are not warranted. Given the potential high value of this information and the scope and cost of the prospective longitudinal databases, new approaches to funding these natural history studies should be considered, including use of funds from the prescription drug user fee act for prospective studies of rare diseases relevant to new advances from the pharmaceutical industry.

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Figure Legends

Figure 1. Application of Inclusion and Exclusion Criteria to the LOGIC Cohort. From 252 of the 1261 LOGIC participants who had a diagnosis of Alagille syndrome, 59 participants could be identified who met the applicable inclusion and exclusion criteria of ITCH.

Figure 2. Heatmap of Change in Clinician Scratch Scale (CSS) from Baseline. Colors as noted in the legend indicate the change in CSS. Figure 2A. The percentage of the total number of participants with each of the specified changes (note -4 is the maximal reduction in CSS that is possible) is shown at year-1 and year-2 of follow up. Figure 2B. The absolute number of participants with a given change (note the minimal CSS is 0) at year-1 and year-2 is shown relative to their baseline CSS assessment.

Figure 3. Survival with Native Liver. Kaplan-Meier survival curves are shown relative to time from baseline. Figure 3A. Unweighted analysis of all 59 natural history cohort participants. Figure 3B. Weighted analysis of natural history participants. The grey shaded area represents the 95% confidence interval for the measurement.

Figure 1

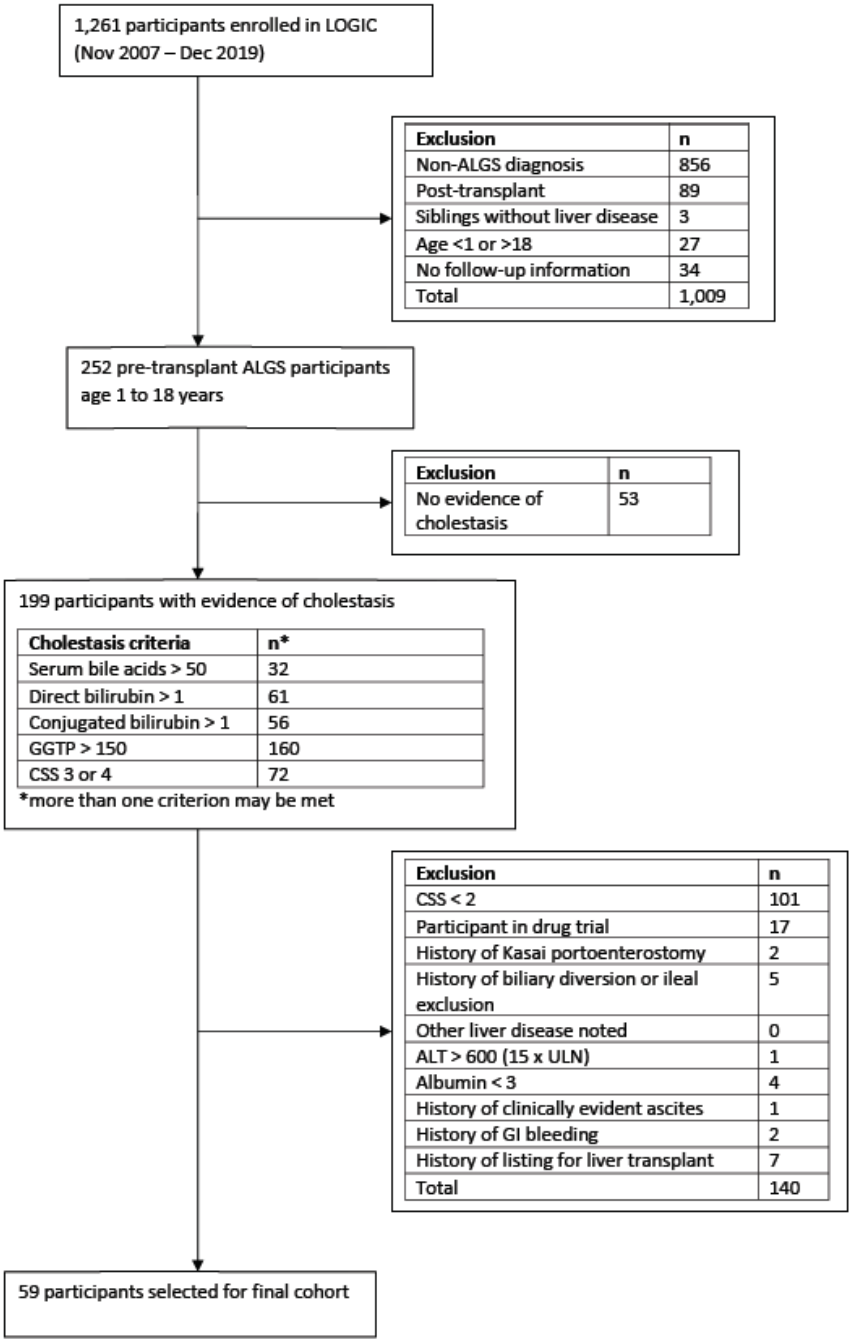


Figure 2a

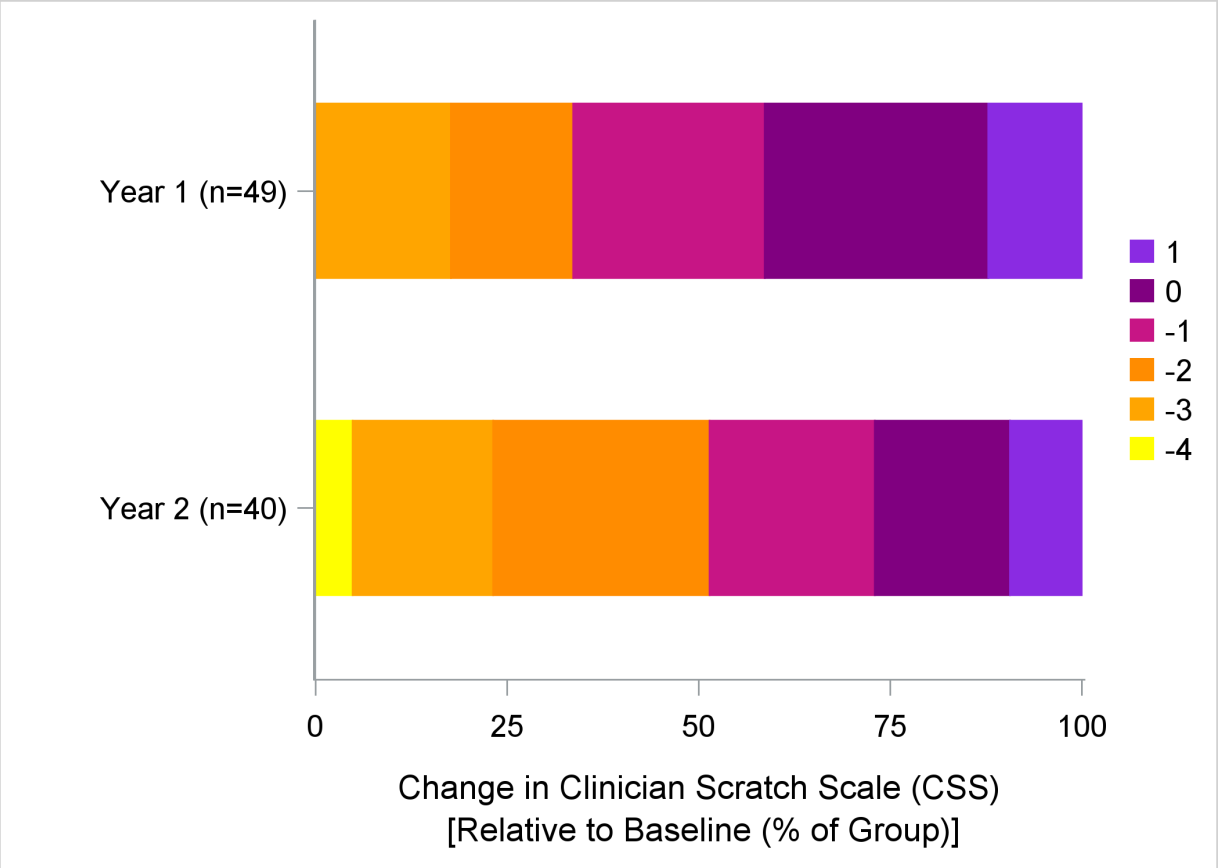


Figure 2b

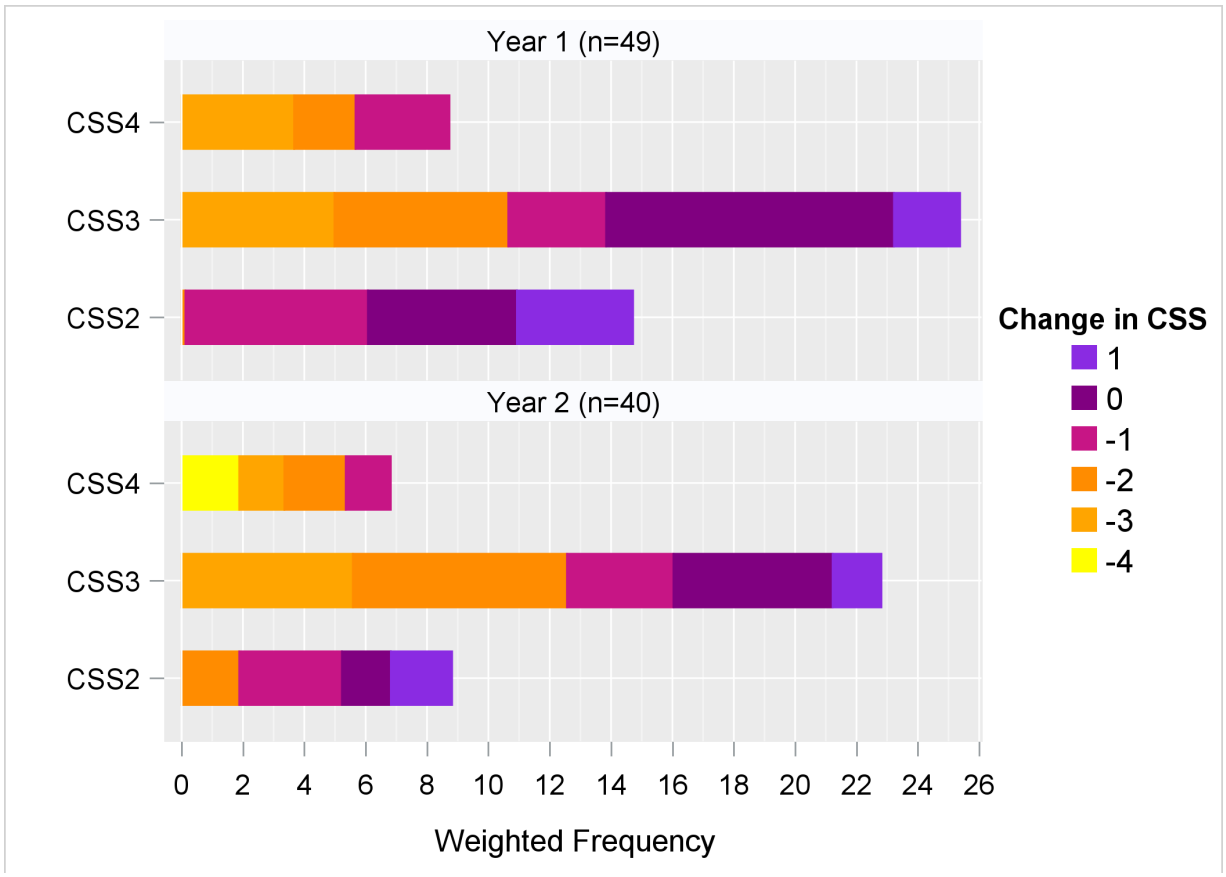
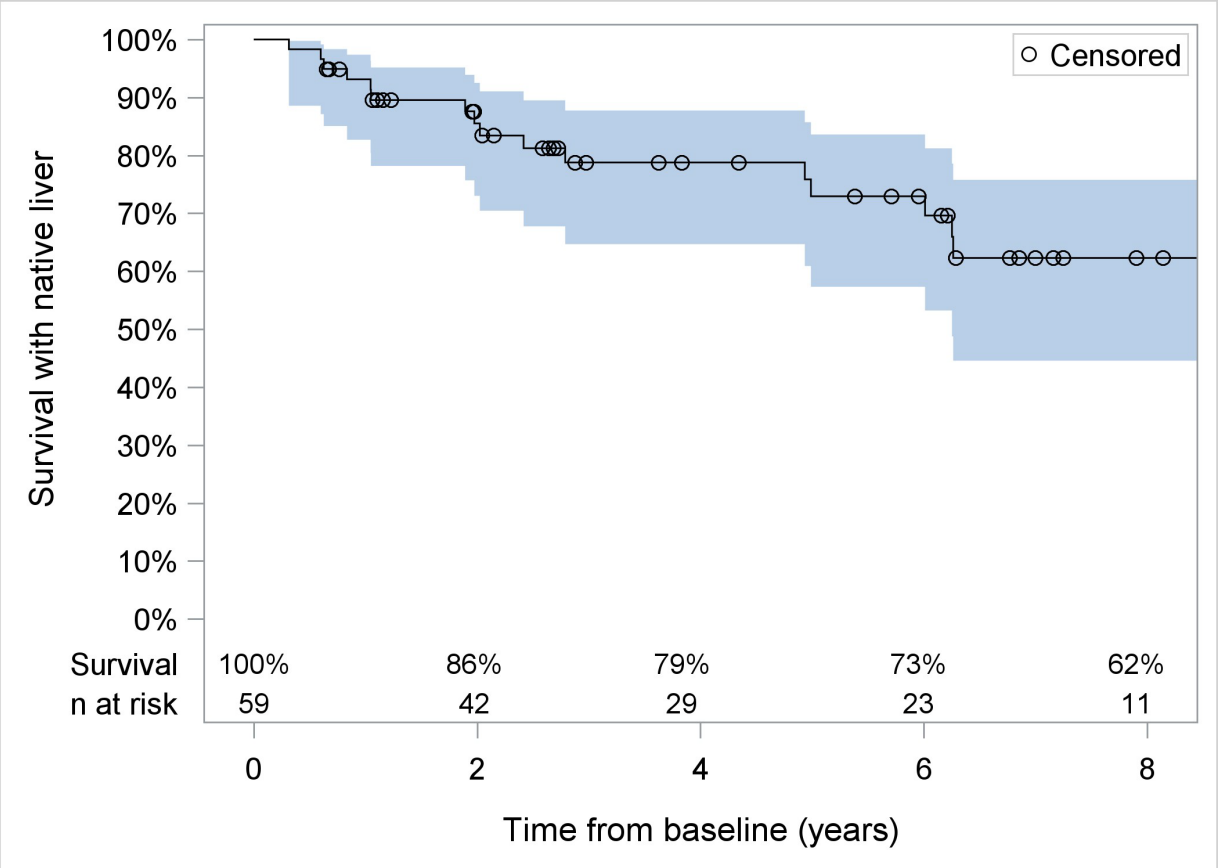


Figure 3 Survival with Native Liver

A. Unweighted survival estimates



B. Weighted survival estimates

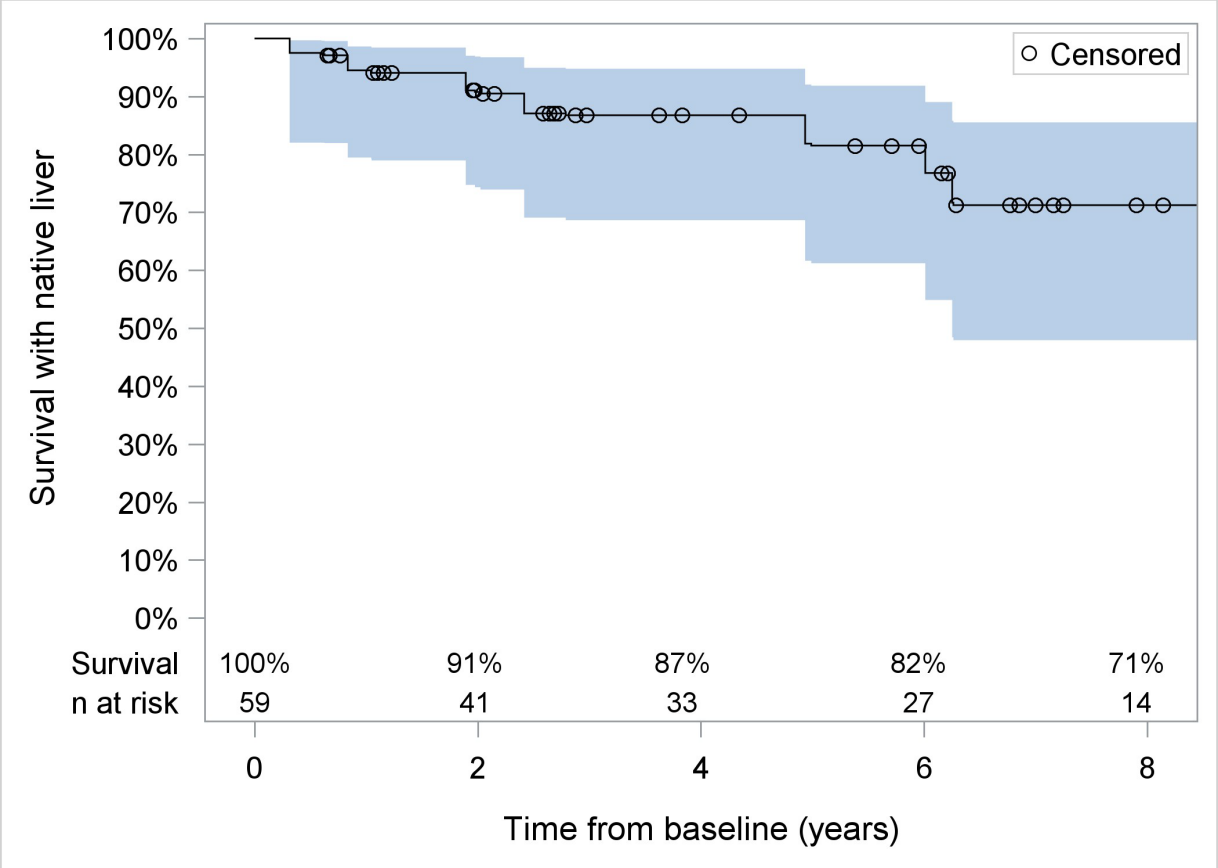


Table 1

Major inclusion/exclusion criteria for ITCH relative to LOGIC ALGS approach

ITCH (from *Hep Comm* 2018;2:1184-1198)	ALGS LOGIC Natural History Cohort
Inclusion Criteria	
Diagnosis of Alagille Syndrome	LOGIC definition of ALGS
Age 12 months – 18 years inclusive	Age 12 months – 18 years inclusive
Cholestasis Total Serum Bile Acid > 3X ULN for age or Direct bilirubin > 1 mg/dL or Fat soluble vitamin deficiency or GGT > 3X ULN for age or Intractable pruritus based on liver disease	Cholestasis Total Serum Bile Acids > 50 µM or Direct bilirubin or conjugated bilirubin > 1 mg/dL or Not applied or GGT > 150 IU/L or Clinical scratch scale score of 3 or 4
Pruritus – average daily ItchRO (obs) $\geq$ 2.0	Clinician scratch scale score $\geq$ 2.0
Exclusion Criteria	
Chronic diarrhea requiring intravenous fluids	Not applied
Surgical interruption of the enterohepatic circulation	From LOGIC history for surgery
Liver transplant	From LOGIC history for surgery
ALT > 15 x ULN	ALT > 600 IU/L at baseline
Decompensated cirrhosis INR > 1.5 after vitamin K Albumin < 3.0 gr/dL History of or presence of significant ascites History of variceal hemorrhage History of encephalopathy	Decompensated cirrhosis Not applied – problem ascertaining vitamin K given Albumin < 3.0 gr/dL History of clinically evident ascites History of gastrointestinal hemorrhage Not applied – not available
History of other liver disease	Reviewed historical data – excluded participants with prior kasai hepatoportoenterostomy and diagnosis of biliary atresia
History of disease that could interfere with absorption of drugs, bile acids, etc. from intestine	Not applied – data unavailable but unlikely
Unable to complete study	Listed for liver transplant
Concomitant meds – cholestyramine or other resin, sodium phenylbutyrate, investigational agent trial	Applied as known
Nonadherence concern	Not applied

Table 2

Comparison of Baseline parameters of ITCH participants and LOGIC ALGS Natural History Cohort

	ITCH *All Participants*	LOGIC ALGS Natural History Cohort *(unweighted)*		LOGIC ALGS Natural History Cohort *(weighted)*	
N	37	59		59	
	Summary statistics – mean (SD) [n], median	Summary statistics	SMD% (p-value*)	Summary statistics	SMD% (p-value‡)
Age, years	6.8 (4.5) [37], 6.0	4.1 (3.2) [59], 2.5	69% (<0.001)	6.2 (3.1) [59], 6.5	16% (0.32)
Age			(<0.001)		(1.00)
< 2 years	2 (5%)	26 (44%)		3.2 (5%)	
2 to 4 years	12(32%)	13 (22%)		19.1 (32%)	
5 to 7 years	11 (30%)	10 (17%)		17.5 (30%)	
8 to 18 years	12 (33%)	10 (17%)		19.1 (32%)	
Gender			(1.00)		(0.63)
Female	16 (43%)	25 (42%)		22.2 (38%)	
Male	21 (57%)	33 (56%)		36.7 (62%)	
Not reported		1 (2%)		0.1 (0.2%)^	
Race			(0.053)		(0.16)
White	29 (78%)	30 (51%)		33.7 (57%)	
Black	5 (14%)	13 (22%)		9.3 (16%)	
Non-White, Non-Black	2 (5%)	9 (15%)		11.1 (19%)	
Not reported	1 (3%)	7 (12%)		4.9 (8%)	
Ethnicity			(0.63)		(0.91)
Hispanic	7 (18.9%)	9 (15%)		11.7 (20%)	
Non-Hispanic	30 (81%)	48 (81%)		47.0 (80%)	
Not reported		2 (3%)		0.2 (0.4%)^	
ItchRO	2.9 (0.60) [37], 2.9				
Clinician Scratch Score, range 0-4	3.0 (1.1) [37], 3.0	2.9 (0.7) [59], 3.0	11% (0.47)	2.8 (0.7) [59], 2.4	22% (0.16)
PedsQL Parent Total Score, range 0 - 100	65 (20.1) [35], 67	78.8 (12.86) [21], 84.7	-82% (<0.001)	79.0 (9.7) [21], 83.1	-89% (<0.001)
Total Bilirubin (mg/dL) [3]	5.3 (6.18) [37], 2.1	4.9 (5.42) [57], 2.3	7% (0.67)	3.7 (5.2) [57], 1.4	28% (0.07)
Cholesterol (mg/dL)	405.7 (313.6) [37], 320	522.4 (342.6) [24], 454	-36% (0.06)	408.1 (151.8) [24], 301.4	-1% (0.94)
Serum Bile Acid (umol/L)	216.3 (203.3) [37], 155.5	174.2 (9.0) [14], 179.2	27% (0.14)	147.5 (29.9) [14], 160.0	47% (0.007)
ALT (IU/L)	158.7 (86.5) [37], 137	196.7 (99.5) [57], 187	-41% (0.007)	184.7 (109.2) [57], 163.9	-26% (0.07)
GGT (IU/L)	494.9 (379.8) [37], 329	542.1 (460.4) [54], 388	-11% (0.45)	495.6 (439.6) [54], 292	0% (0.99)
Albumin (g/dL)	4.5 (0.4) [37], 4.6	4.1 (0.4) [57], 4.1	95% (<0.001)	4.2 (0.4) [57], 4.1	76% (<0.001)
Platelets (10^3/mm^3)	287.0 (109.5) [37], 258	308.0 (110.4) [51], 308	-19% (0.214)	289.7 (105.9) [51], 263.7	-3% (0.87)
Height Z-score	-1.6 (1.2) [37], -1.6	-2.3 (1.3) [58], -2.3	59% (<0.001)	-1.9 (1.0) [58], -2.0	26% (0.09)
Weight Z-score	-1.3 (1.1) [37], -1.3	-1.7 (0.9) [58], -1.7	39% (0.01)	-1.5 (0.9) [58], -1.4	17% (0.26)

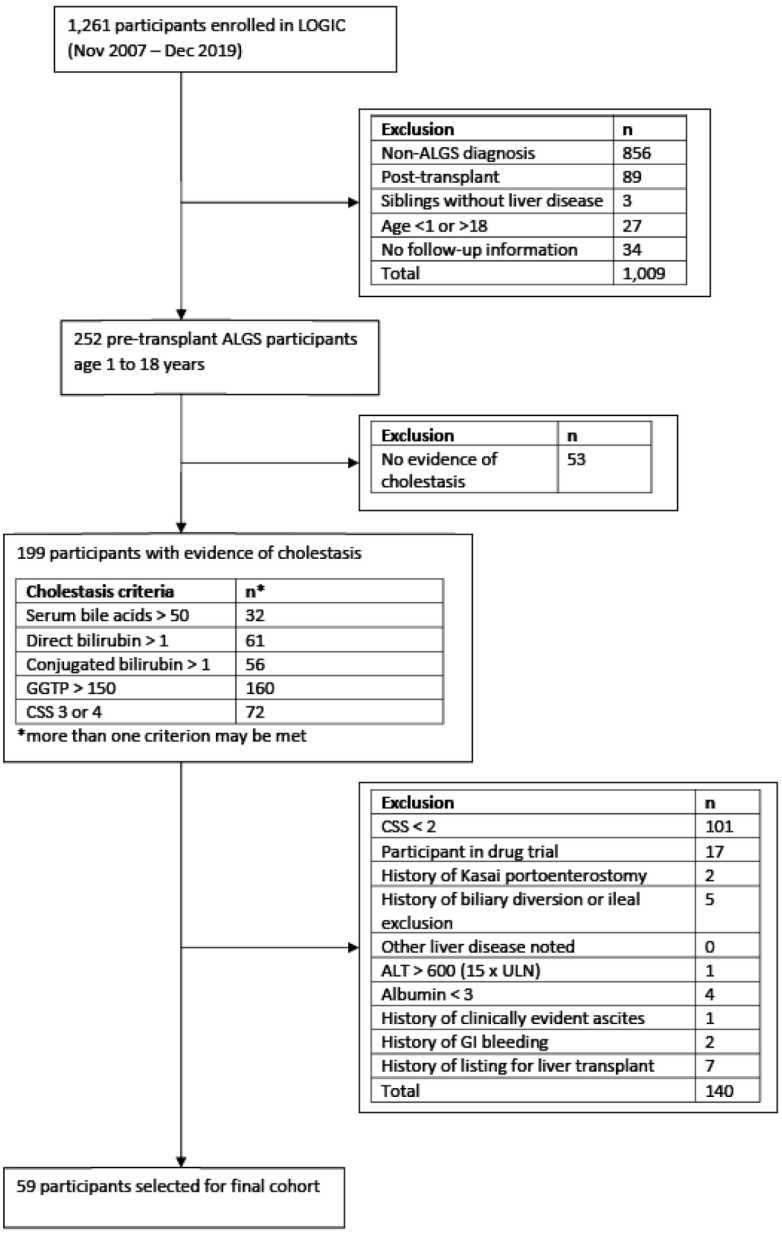
* SMD = standardized mean difference

Table 3

Change from Baseline for Key Parameters

	Year 1 - Baseline (n=50)			Year 2 - Baseline (n=40)		
	n	Weighted mean change (SE)	95% CLM	n	Weighted mean change (SE)	95% CLM
Clinician Scratch	49	-0.98 (0.24)	**(-1.47, -0.49)**	40	-1.43 (0.28)	**(-1.99, -0.87)**
Total bilirubin (mg/dL)	44	1.20 (0.91)	(-0.64, 3.03)	36	0.02 (0.30)	(-0.58, 0.62)
ALT (IU/L)	44	-15.8 (13.4)	(-42.8, 11.2)	36	5.7 (14.3)	(-23.4, 34.8)
Platelets (x 10 3)	40	-19.2 (9.8)	(-39.0, 0.6)	30	-65.2 (16.2)	**(-98.3, -32.1)**
Albumin (g/dL)	43	0.09 (0.07)	(-0.04, 0.22)	35	0.09 (0.09)	(-0.09, 0.28)
Weight (z-score)	49	0.14 (0.08)	(-0.02, 0.29)	40	0.17 (0.13)	(-0.08, 0.43)
Height (z-score)	48	0.23 (0.07)	**(0.08, 0.37)**	39	0.28 (0.10)	**(0.08, 0.48)**

* bolded numbers are statistically significant changes, CLM = Confidence limit for the measurement



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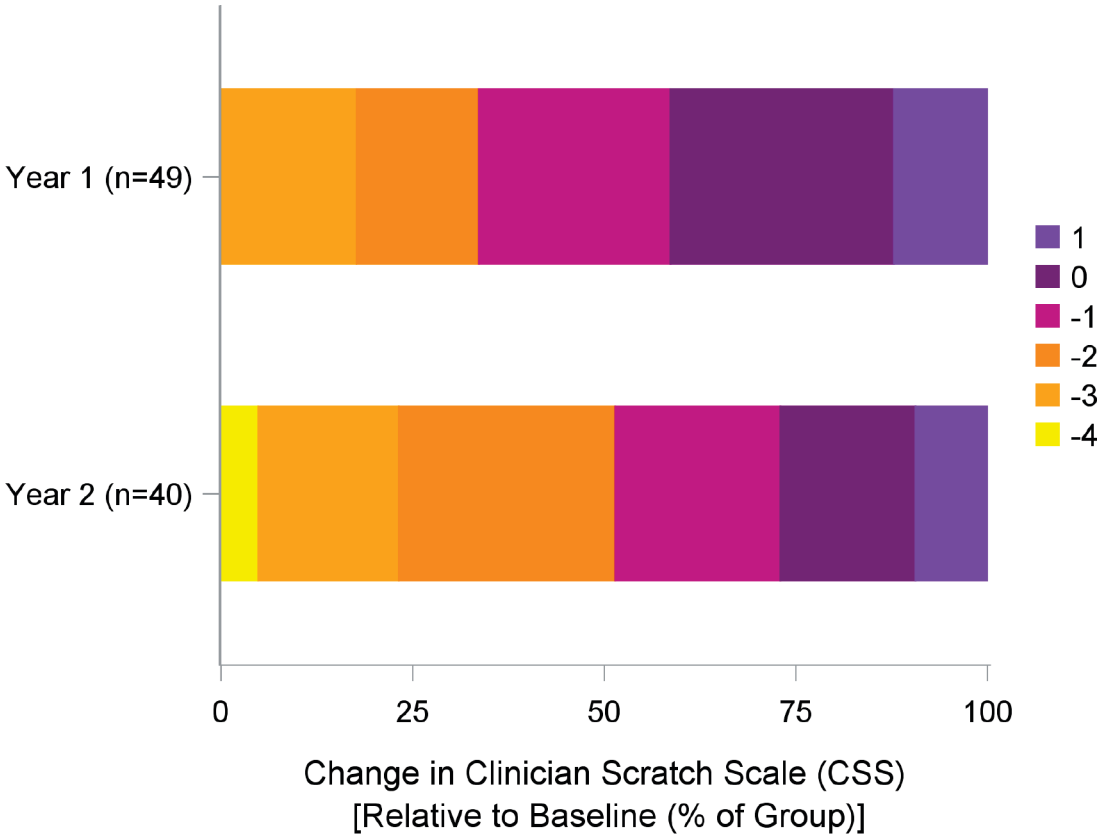

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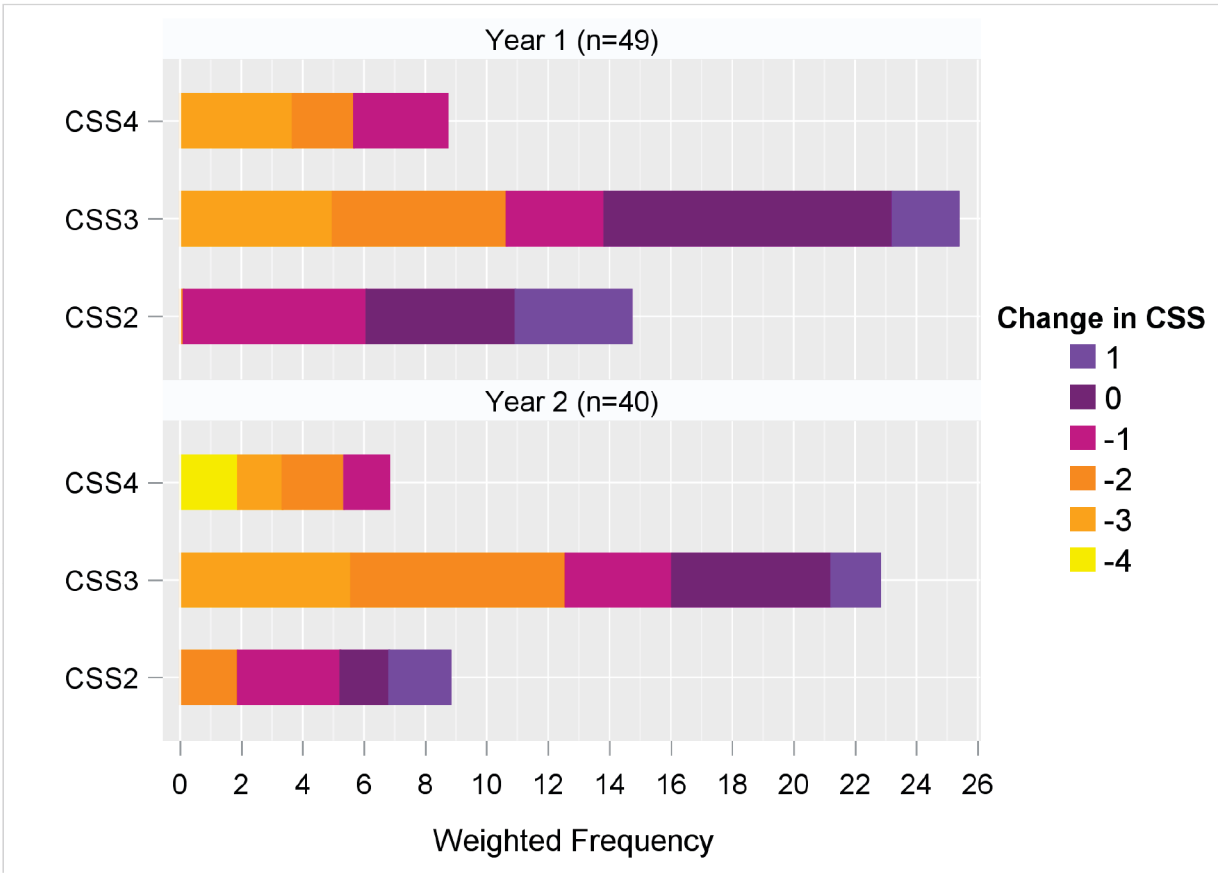

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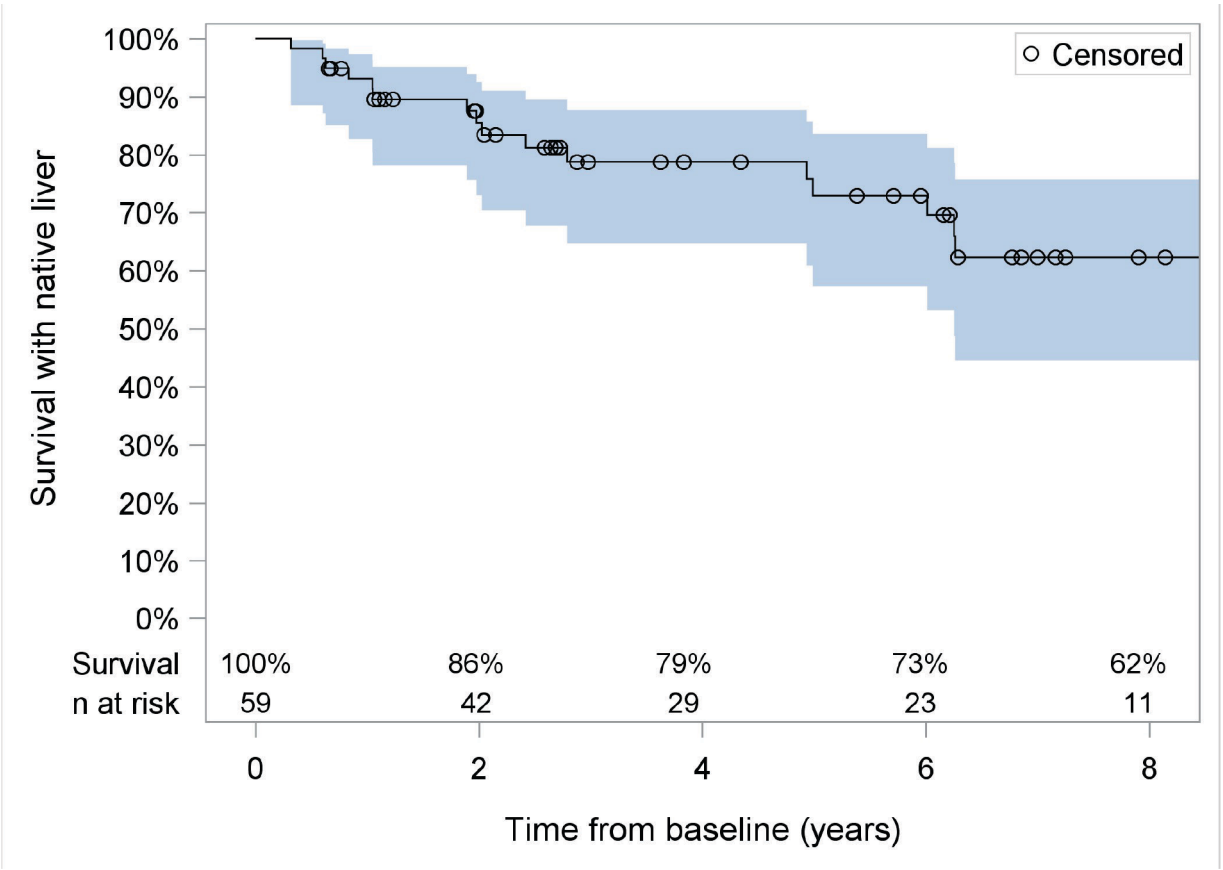

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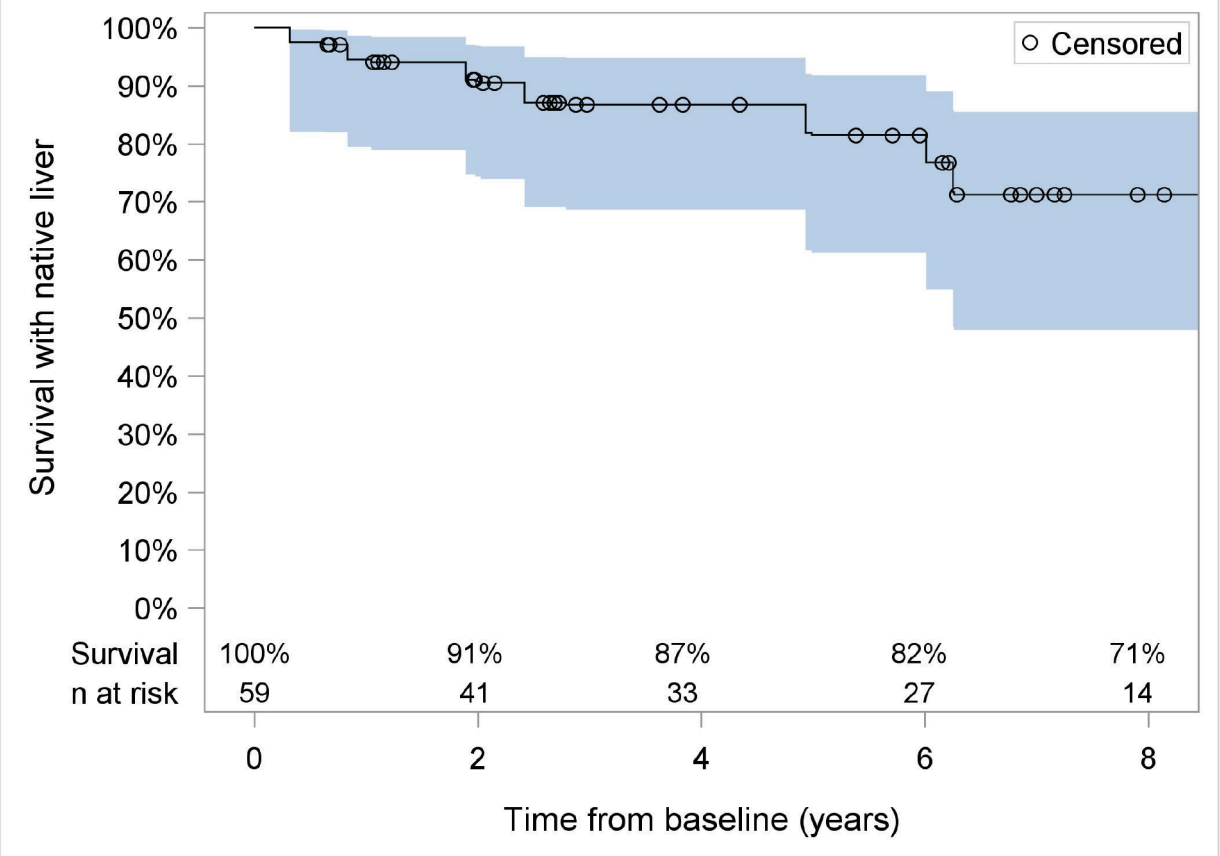

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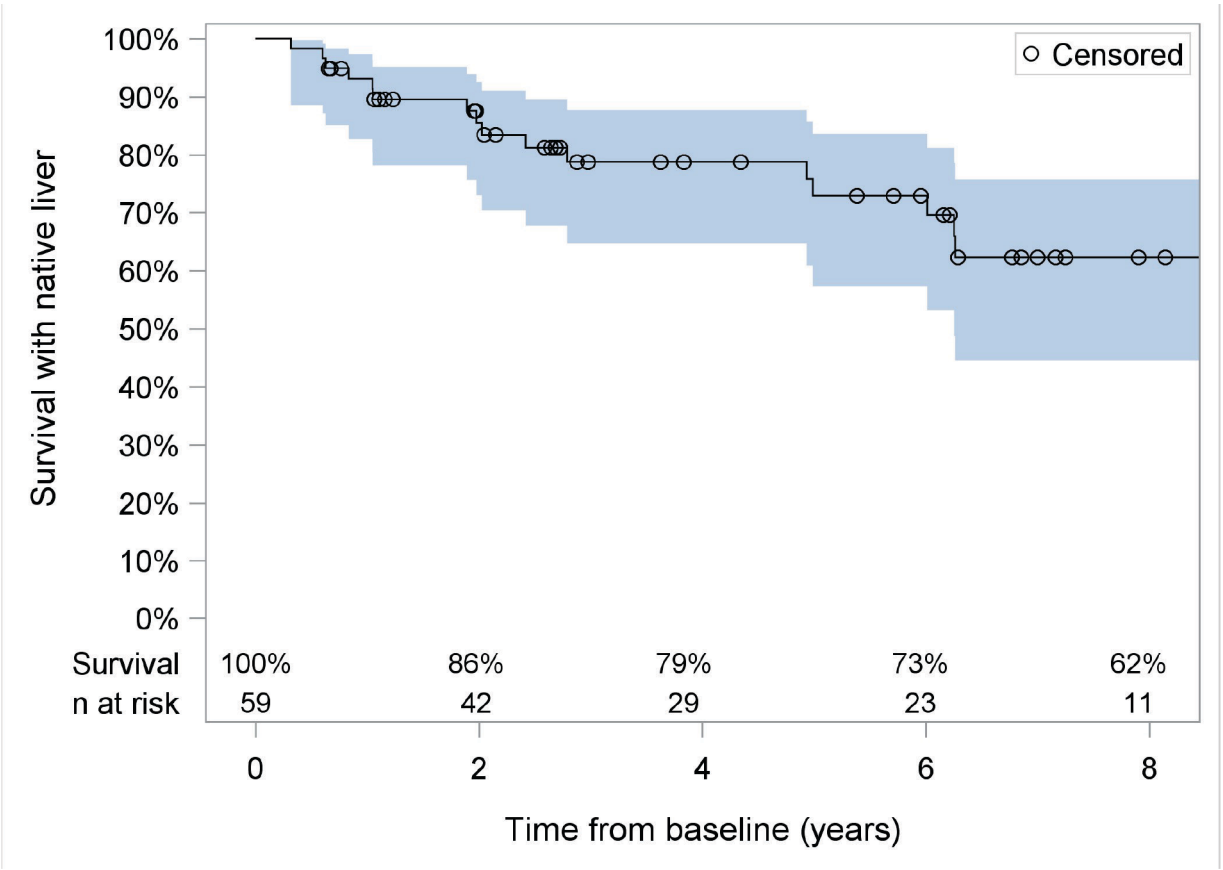

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The current studies have shown that prospective longitudinal database registries can be utilized to provide important and unique contextual information regarding interventional clinical trials in rare diseases. Given the potential high value of this information and the scope and cost of the prospective longitudinal databases, new approaches to funding these natural history studies should be considered, including use of funds from the prescription drug user fee act for prospective studies of rare diseases relevant to new advances from the pharmaceutical industry.