

# Application of real-world evidence analytics: A 6-year event-free survival analysis in Alagille syndrome of the GALA clinical research database and maralixibat treated patients



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# Bettina E. Hansen, PhD

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- She holds the Francis Family Chair in International Biostatistics Research for Autoimmune Liver Disease.
- Dr. Hansen leads large-scale clinical research projects related to chronic hepatitis, auto-immune liver diseases and rare liver diseases in children. Her work initiating multiple international studies, and novel application of sophisticated statistical tools have transformed the understanding, clinical management, and treatment of liver conditions around the world.



# Disclosures

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## Bettina E. Hansen, PhD

I disclose the following financial relationship(s) with a commercial interest:

- Mirum: Grant/Research Support, Consulting
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- Calliditas: Grant/Research Support, Consulting
- Albireo: Grant/Research Support, Consulting
- Genfit: Consulting
- Chemomab: Consulting
- Novartis: Consulting
- ENYO Pharma: Consulting
- Eiger: Consulting

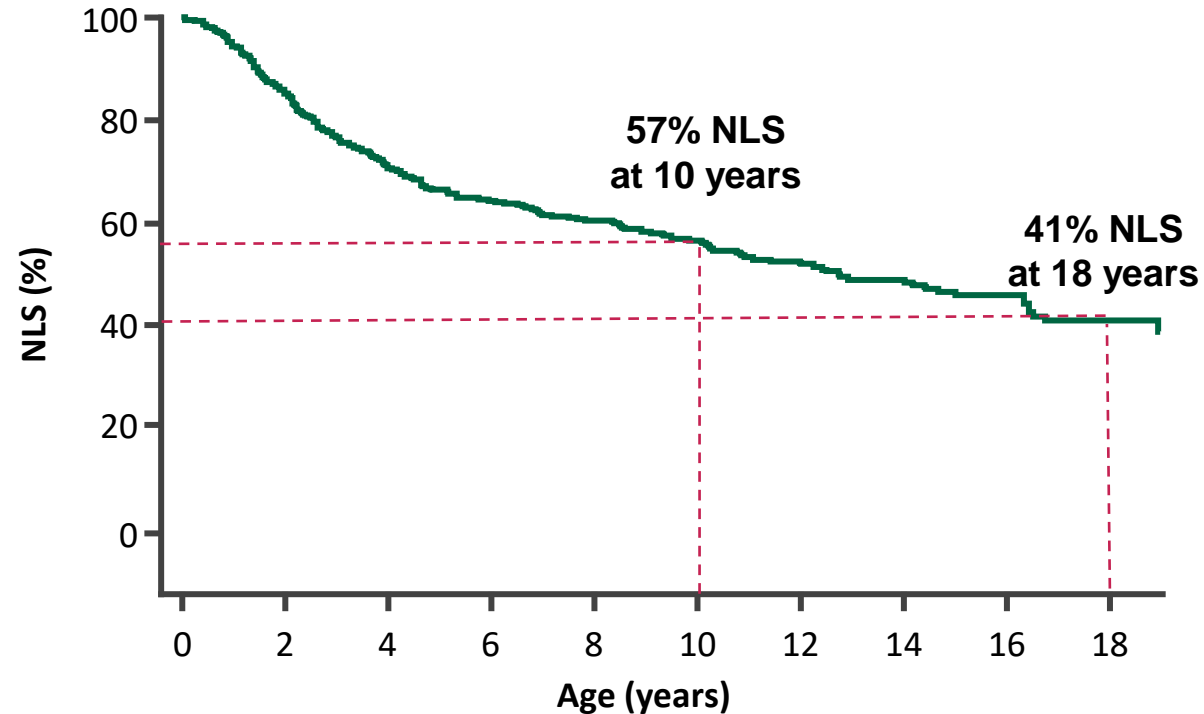
# Alagille syndrome: Background

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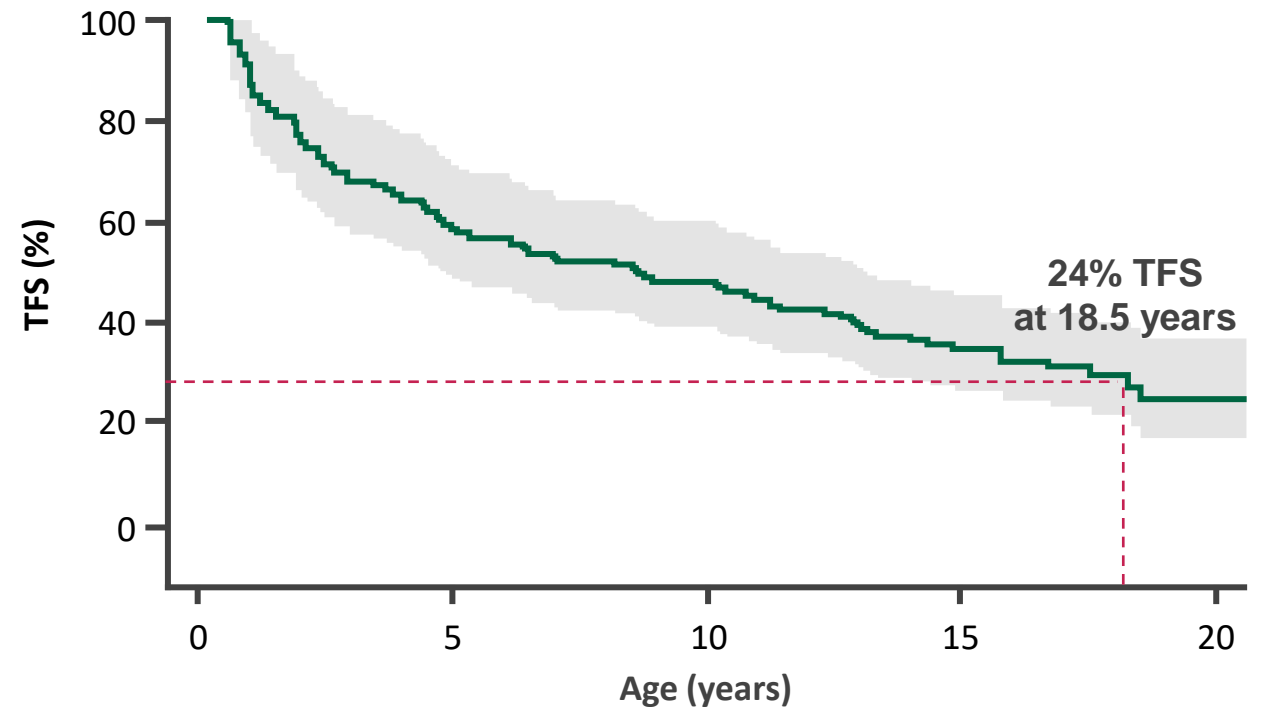
- Alagille syndrome (ALGS) is a rare, autosomal dominant developmental disorder characterized by bile duct paucity and extrahepatic clinical manifestations
- Key clinical features of ALGS are cholestasis, xanthomas and severe debilitating pruritus
- Complications of cholestasis and severe pruritus are the leading indications for liver transplantation
- Transplant-free survival is 24%–41% at 18.5 years of age<sup>1,2</sup>

# Substantial risk for liver transplant in patients with ALGS

**GALA<sup>1</sup> (Global)**  
Native liver survival (NLS) in patients with ALGS  
presenting with neonatal cholestasis (N=911)



**ChiLDReN (North America network)<sup>2</sup>**  
Transplant-free survival (TFS) in patients with ALGS (N=293)

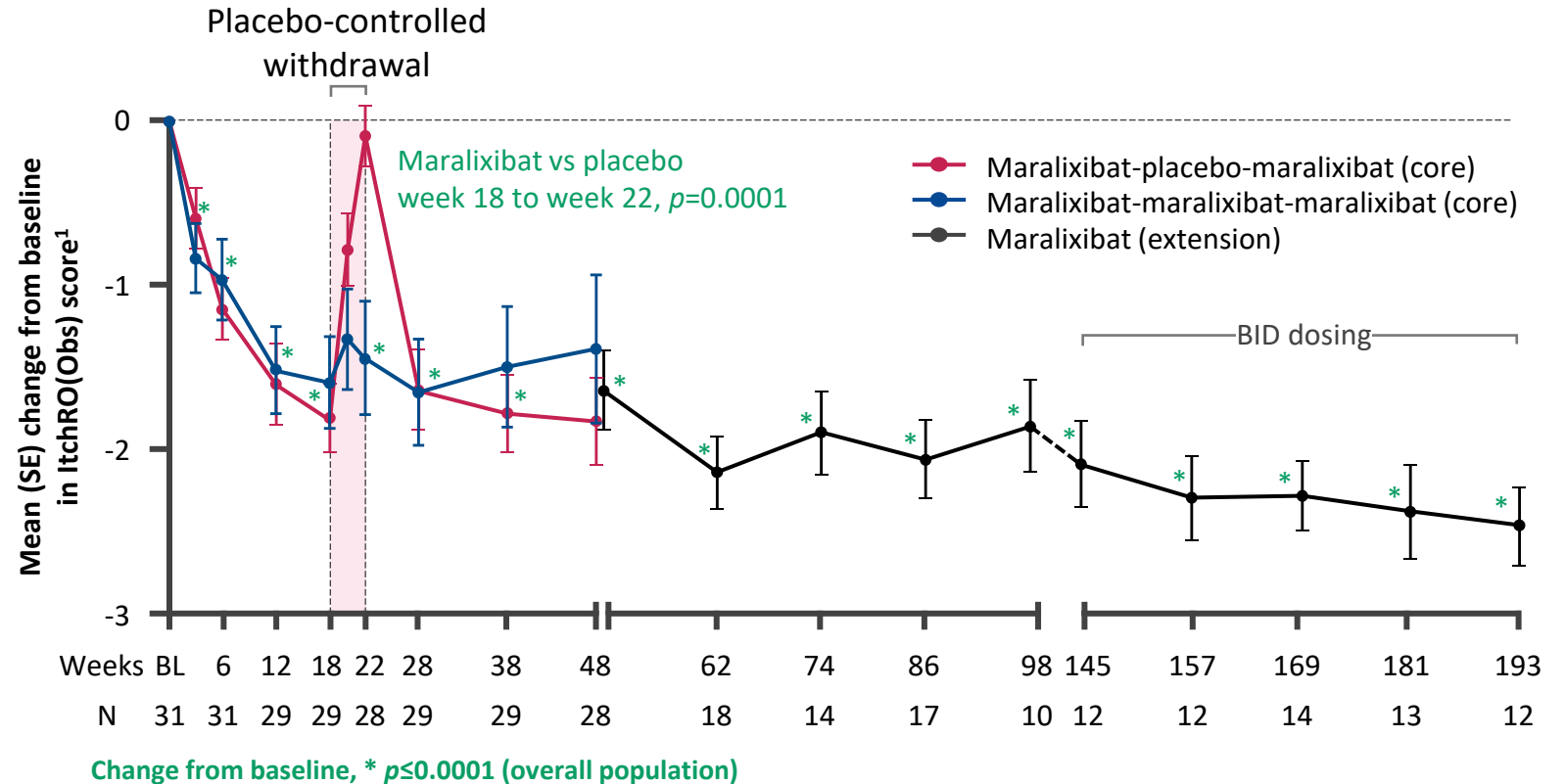
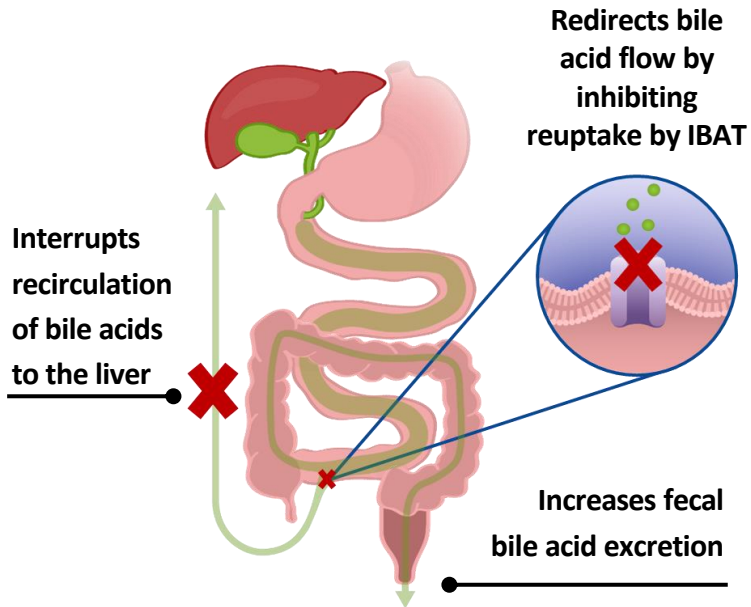


Native Liver Survival = Transplant-Free Survival

1. Vandriel SM, et al. EASL 2020 (poster presentation); 2. Kamath BM, et al. *Hepatol Comms* 2020; 4:387–398.

# Maralixibat is an Ileal Bile Acid Transporter (IBAT) inhibitor that interrupts bile acid recirculation and significantly improves pruritus<sup>1,2</sup>

Interrupts recirculation of bile acids to the liver<sup>1</sup>



**Maralixibat (Livmarli™) recently received FDA approval for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older<sup>1,2</sup>**

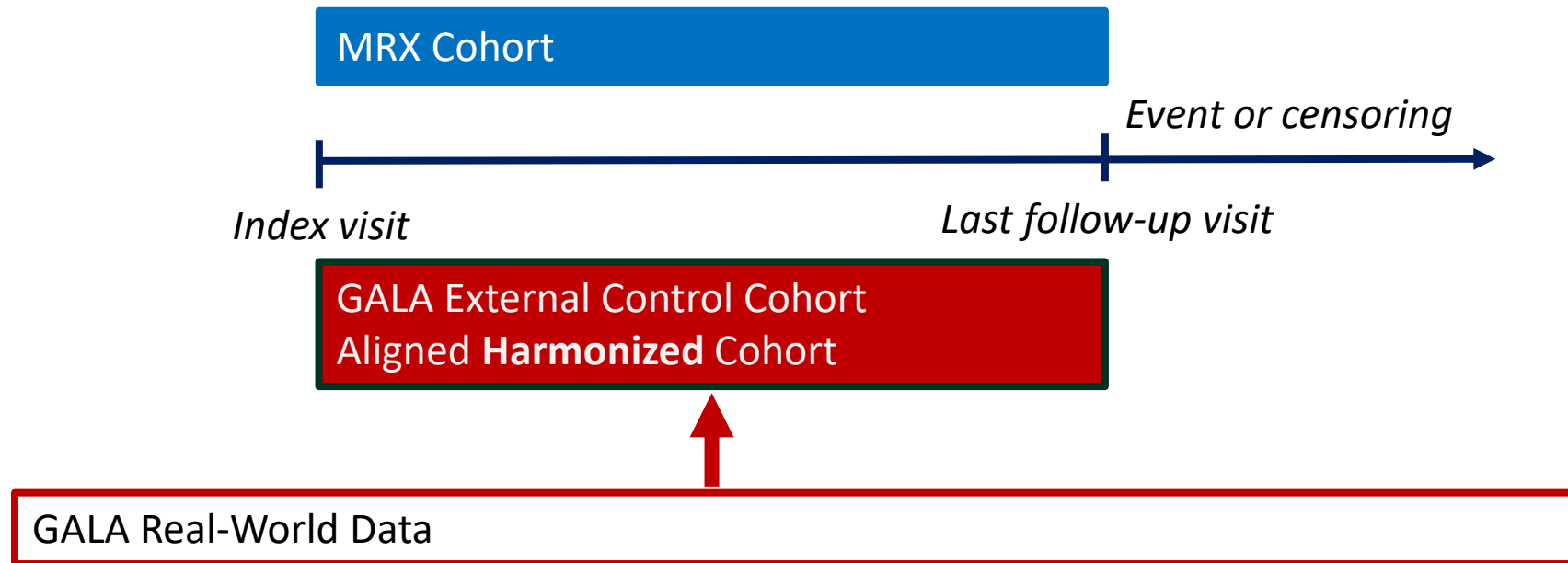
FDA, United States Food and Drug Administration; IBAT(i), ileal bile acid transporter (inhibitor).

1. Gonzales E, et al. *Lancet* October 2021; Vol 398; 2. Mirum Pharmaceuticals, Inc. LIVMARLI™ (maralixibat) Prescribing Information. 2021.

Accessed online at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/214662s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214662s000lbl.pdf) on October 18, 2021.

# Primary objective

- To compare time to first clinical event between a maralixibat (MRX) cohort of 84 patients treated for up to 6 years and an external control cohort from the GALA database
  - Events defined as: liver transplantation; biliary diversion surgery; decompensation event (ascites requiring therapy or variceal bleeding); or death



# Challenges in clinical research for rare diseases

- Long-term, randomized controlled trials with definitive clinical outcomes are difficult, if not impossible, to conduct in rare diseases
- Use of Real-World Data as a control arm is a potential alternative to assess long-term outcomes. Challenges to overcome include variations in:
  - Baseline characteristics
  - Disease severity and trajectory
  - Background standard of care
  - Inherent bias of participating in a clinical trial
- High bar of standardization and quality of Real-World Data<sup>1</sup>

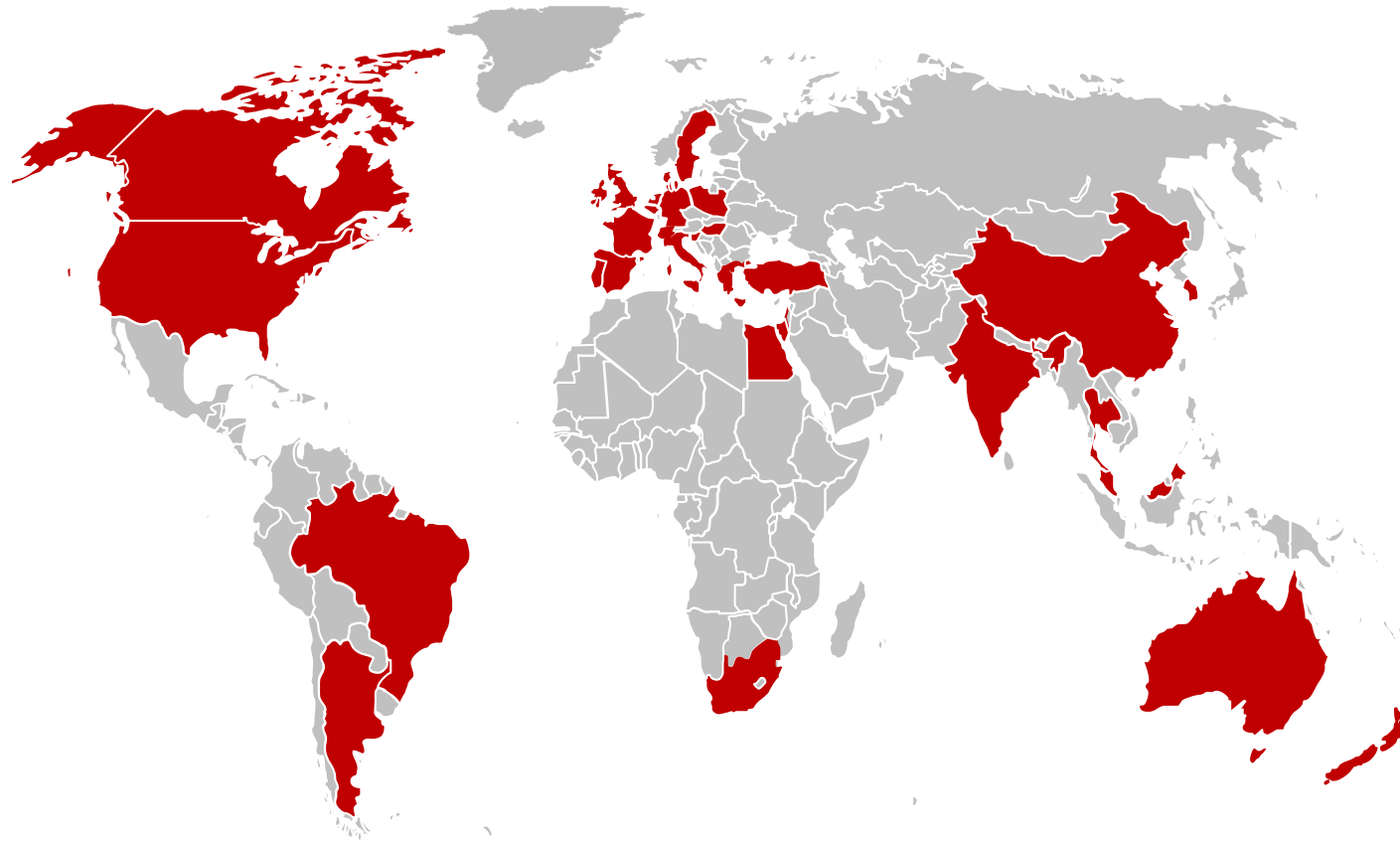
1. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory>. Accessed on November 2, 2021.



# GALA: the only global clinical research database of children and young adults with ALGS



Currently, >1,600 patients with ALGS from 35 countries



# Pre-specified statistical method I: Harmonize design

Firewall on blinded for outcome

## Fit for purpose

- Outcome, confounders
- Quality of lab-values, patient and disease factors, missingness

## Selection

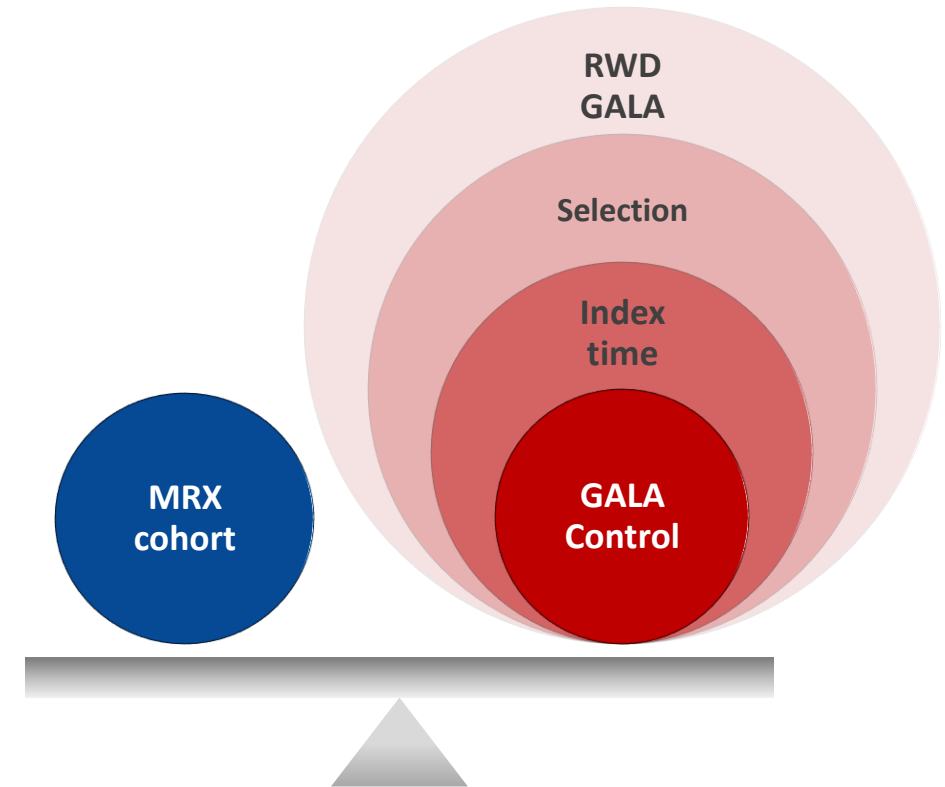
- Align inclusion/exclusion criteria
- Overlay sites / regions / calendar time

## Index Time = Start of follow-up

- Maximum Likelihood Method: best fit
- First visit, random visit(s), last visit

## Assessment of balance

- Pre-specified check and test
- Weights: propensity scores, std IPTW, ATT



# Pre-specified statistical method II: Analysis of time to event

Firewall off  
un-blinded for outcome

## Treatment arm

- Check for informative censoring

## Composite endpoint

- Characterize type of events over time in both Treatment arm and Real-World Data selection

## Analysis of endpoint

- Kaplan-Meier & Cox regression methods
- Crude effect
- Weighted
- Adjusted for confounders

## Sensitivity analyses

- Range of selection of index time
- Pruning to avoid immortal time bias

## Subgroup analysis

- Concurrent calendar time
- Same region
- Overlapping sites

# Pre-specified selection criteria to ensure GALA external control cohort was aligned with maralixibat entry criteria

## Key Inclusion Criteria

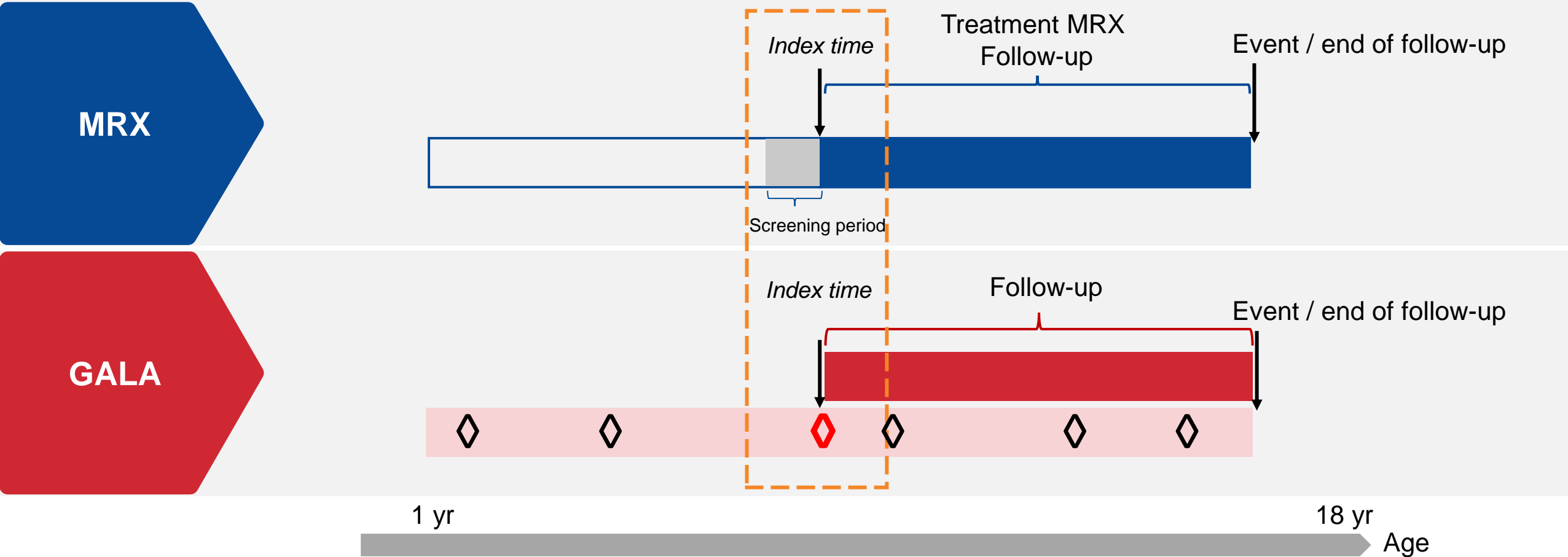
- Age at inclusion:  $\geq 1$  year and  $< 18$  years
- Diagnosed after 1990
- Cholestasis, defined by one or more of the following:
  - Total sBA  $> 3 \times$  ULN
  - Conjugated or direct bilirubin  $> 1$  mg/dL
  - Total bilirubin  $> 2$  mg/dL
  - GGT  $> 3 \times$  ULN

## Key Exclusion Criteria

- ALT  $> 15 \times$  ULN
- Clinical event, defined as BD surgery, liver decompensation (ascites requiring therapy or variceal bleeding), liver transplantation, or death prior to inclusion
- Participation in any intervention clinical study
- Excluded regions in which the MRX ALGS studies were not conducted

**GALA selected primary analysis N = 469; # visits = 3,906**

# Selection of index time: best fit



- ◇ Eligible visit
- ◇ Eligible visit and selection of index time

# Demographic characteristics are well balanced between the maralixibat and GALA groups

Baseline characteristic		MRX Cohort N=84	GALA Control N=469	p-value
Sex, n (%)	Male	49 (58.3)	274 (58.4)	0.988
	Female	35 (41.7)	195 (41.6)	
Age at BL, years	Median (Q1, Q3)	5.6 (2.7, 9.9)	4.3 (2.2, 9.6)	0.078
Year of birth	Mean (Q1, Q3)	2009 (2005, 2012)	2009 (2004, 2013)	0.249
Region, n (%)	Europe	41 (48.8)	229 (48.8)	0.945
	North America	34 (40.5)	195 (41.6)	
	Australia	9 (10.7)	45 (9.6)	
Mutation*, n (%)	<i>JAG1</i>	81 (97.6)	330 (95.1)	0.55
	<i>NOTCH2</i>	2 (2.4)	17 (4.9)	
	Other/unknown	1 (0.2)	37 (9.6)	

BL, baseline; MRX, maralixibat; Q1, first quartile; Q3, third quartile.

\* Due to more than 20% of the cells having expected counts less than 5, chi-square results may be invalid, and Fisher's exact test was used instead.

# Disease characteristics are well-balanced between the maralixibat and GALA groups

Baseline characteristic		MRX Cohort N=84	GALA Control N=469	p-value
Total bilirubin, mg/dL	Median (Q1,Q3)	3.15 (1.00, 8.15)	1.99 (0.60, 11.52)	0.392
	<2 mg/dL	37 (44.0)	235 (50.1)	0.306
	≥2 mg/dL	47 (56.0)	234 (49.9)	
GGT*, U/L	Median (Q1, Q3), log <sub>10</sub> × ULN	1.25 (0.93, 1.44)	1.24 (0.93, 1.52)	0.582
	<3 × ULN	3 (3.6)	6 (1.3)	0.143
	≥3 × ULN	81 (96.4)	463 (98.7)	
ALT, U/L	Median (Q1, Q3)	145 (94, 207)	130 (75, 203)	0.119
sBA†, μmol/L	Median (Q1, Q3)	200 (81, 371) (0% not measured)	125 (39, 260)‡ (85% not measured)	0.003

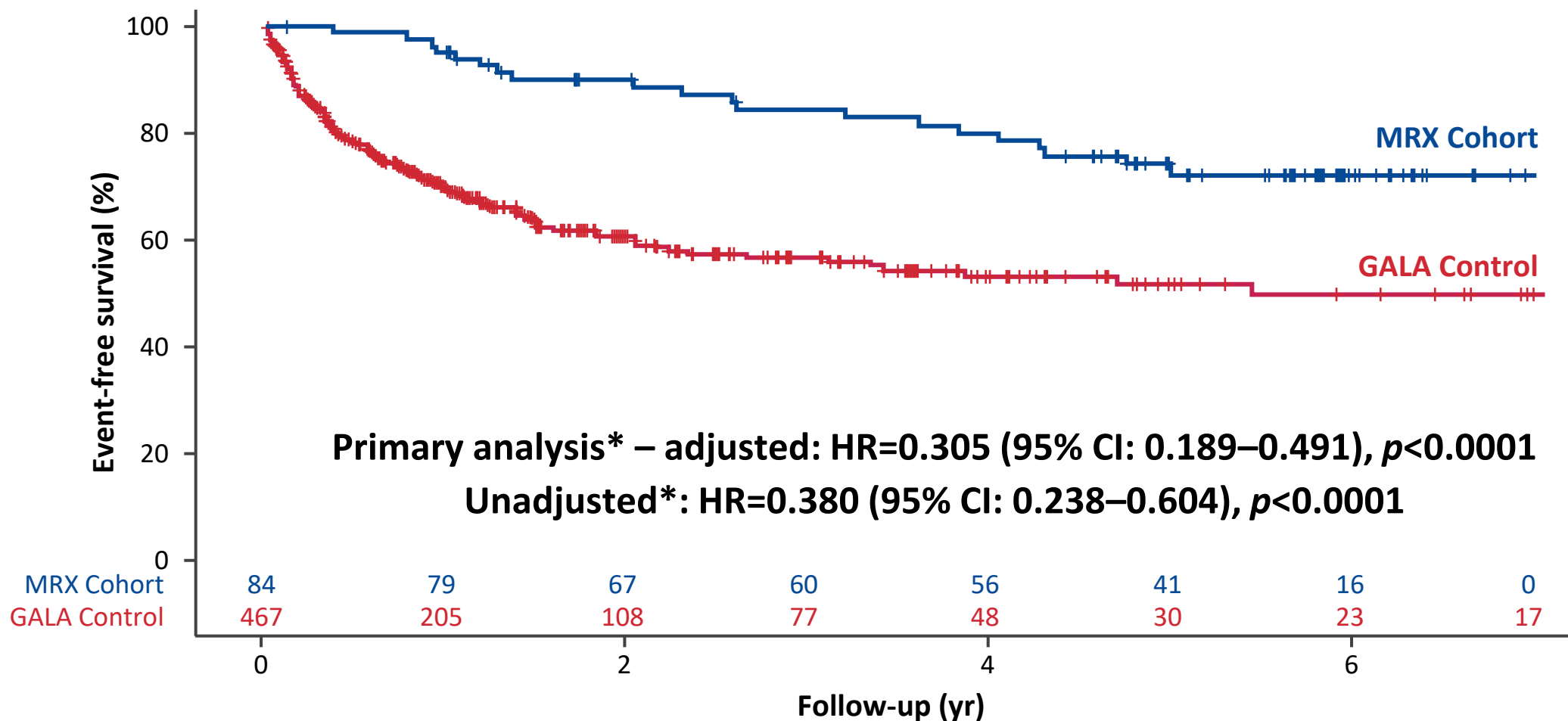
**Key baseline characteristics are well-balanced between the MRX cohort and GALA control group**

ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; MRX, maralixibat; sBA, serum bile acid; ULN, upper limit of normal.

\* Due to more than 20% of the cells having expected counts less than 5, chi-square results may be invalid; † sBA data are limited in the GALA clinical research database since these are not sampled regularly on a clinical basis and Fisher's exact test was used instead. ‡ Baseline sBA was available for 73 participants in the GALA control group.

# Maralixibat shows significant improvement in Event Free Survival

*EFS: biliary diversion surgery, decompensation event, liver transplantation, or death*



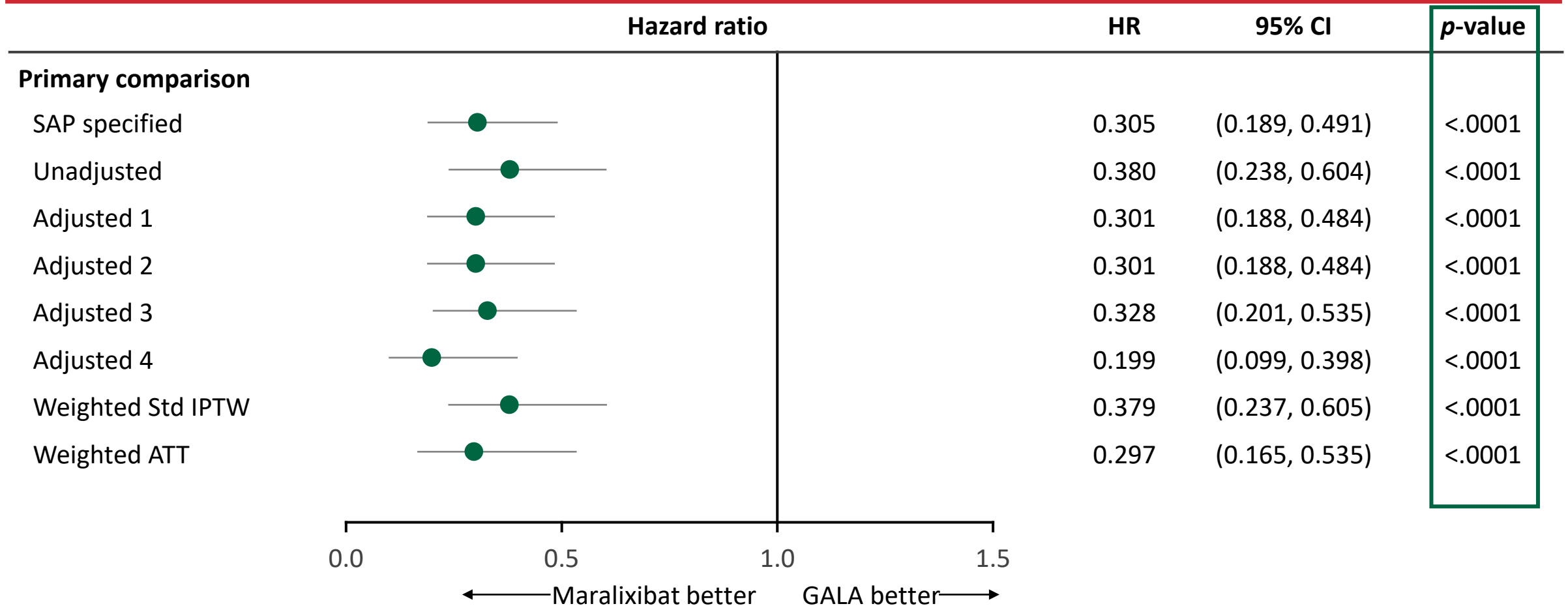
ALT, alanine aminotransferase; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat; SAP, statistical analysis plan.

\* Cox regression models: Primary: Cox regression - effect of MRX vs. GALA log likelihood test adjusted for age, sex, bilirubin, and ALT (according to the SAP).



# Consistent results when adjusting for baseline covariates

Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control



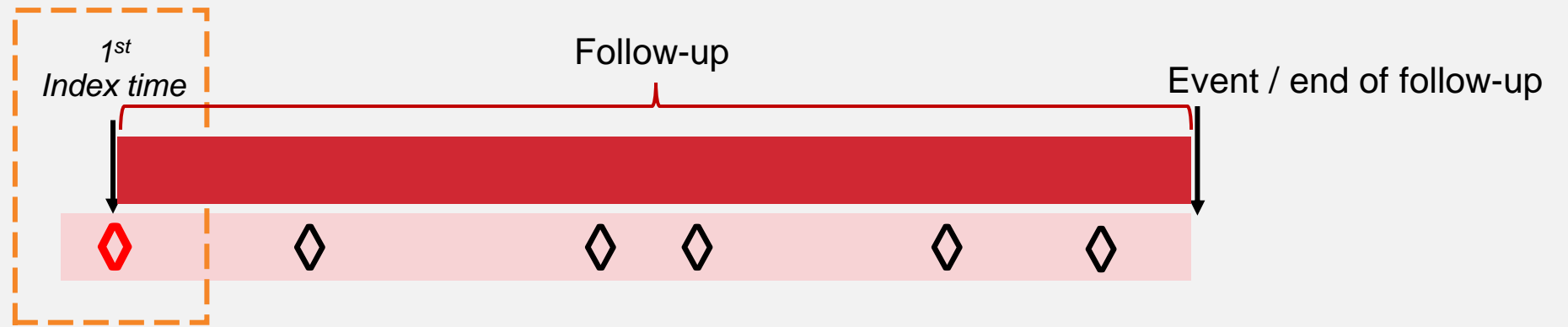
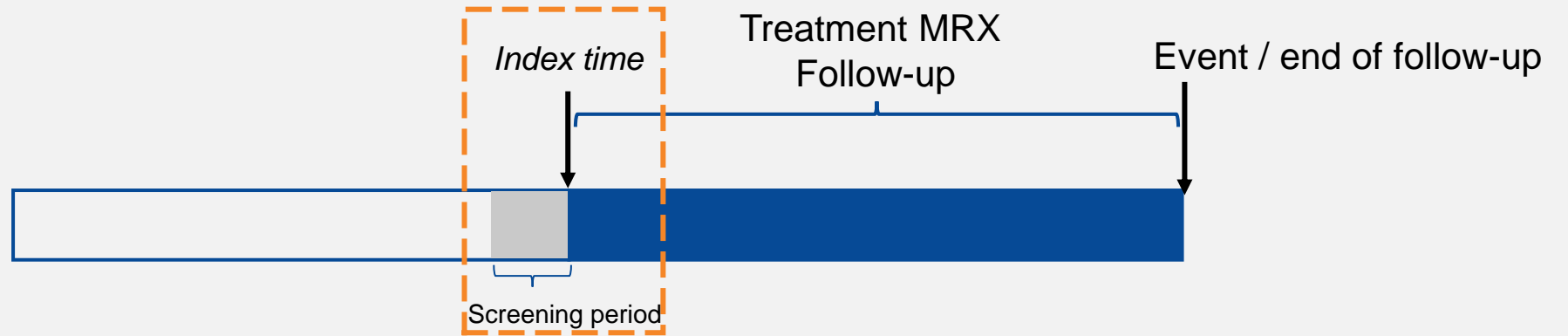
ALT, alanine aminotransferase; ATT, average treatment effect in the treated; CI, confidence interval; EFS, event-free survival; GGT, gamma-glutamyl transferase; HR, hazard ratio; IPTW, inverse probability of treatment weights; SAP, statistical analysis plan; sBA, serum bile acid.

SAP specified: Cox regression adjusted for age, sex, total bilirubin, and ALT; Unadjusted: only covariate being treatment was performed (EFS);

Adjusted 1: Cox regression adjusted for age, total bilirubin, and GGT; Adjusted 2: Cox regression adjusted for age, total bilirubin, GGT, ALT, and region;

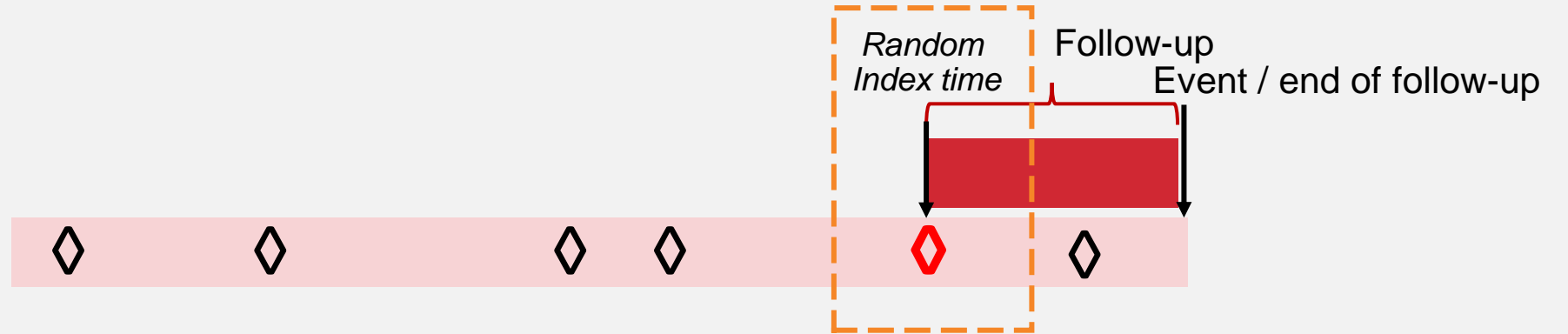
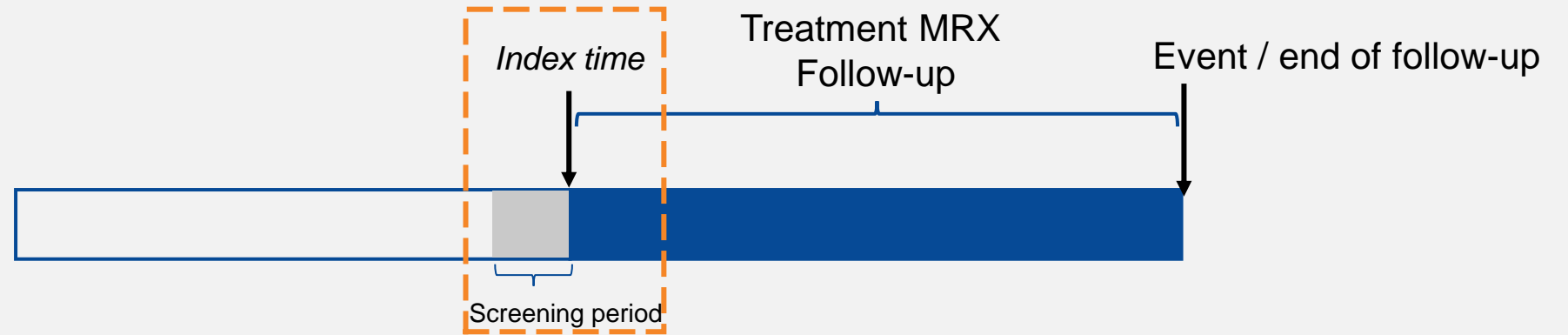
Adjusted 3: Cox regression adjusted for age, total bilirubin, GGT, ALT, sex, and year of birth; Adjusted 4: Cox regression adjusted for age, total bilirubin, GGT, and sBA.

# Selection of index time: first visit



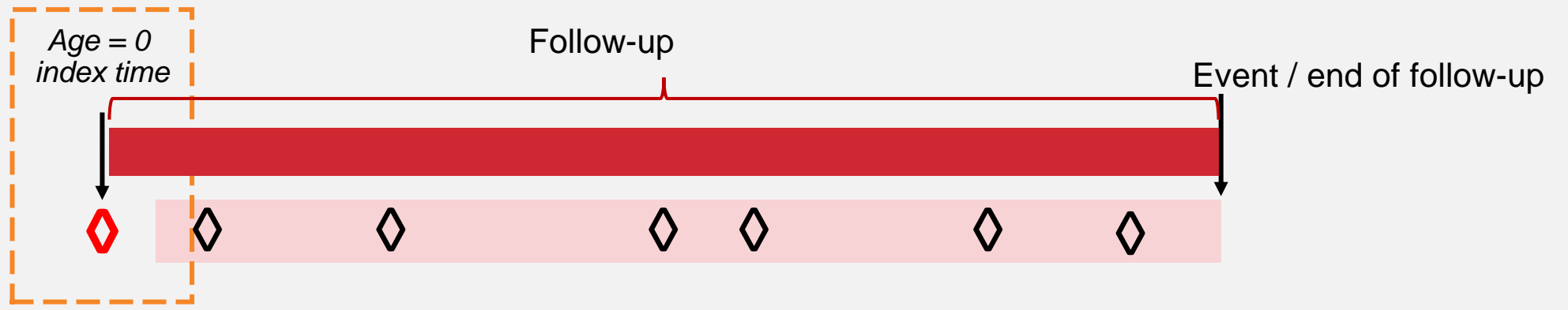
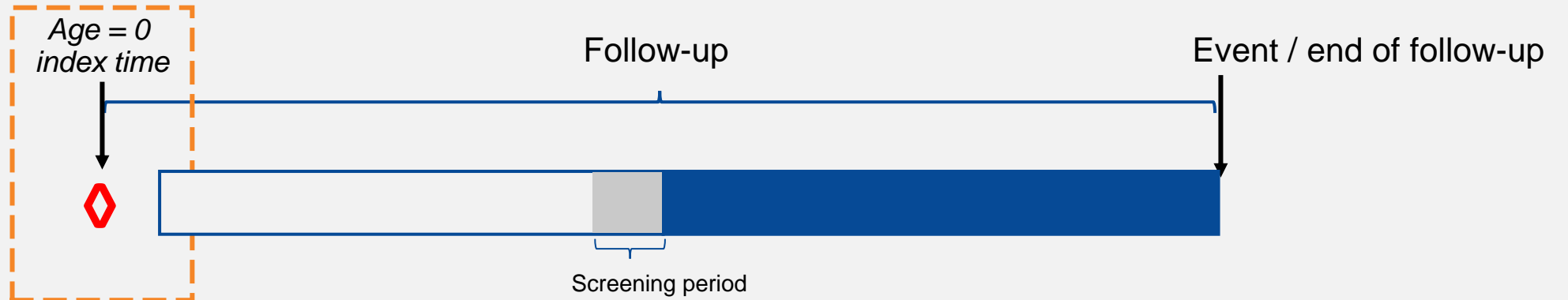
- ◇ Eligible visit
- ◇ Eligible visit and selection of index time

# Selection of index time: random visit



- ◇ Eligible visit
- ◇ Eligible visit and selection of index time

# Selection of index time: date of birth

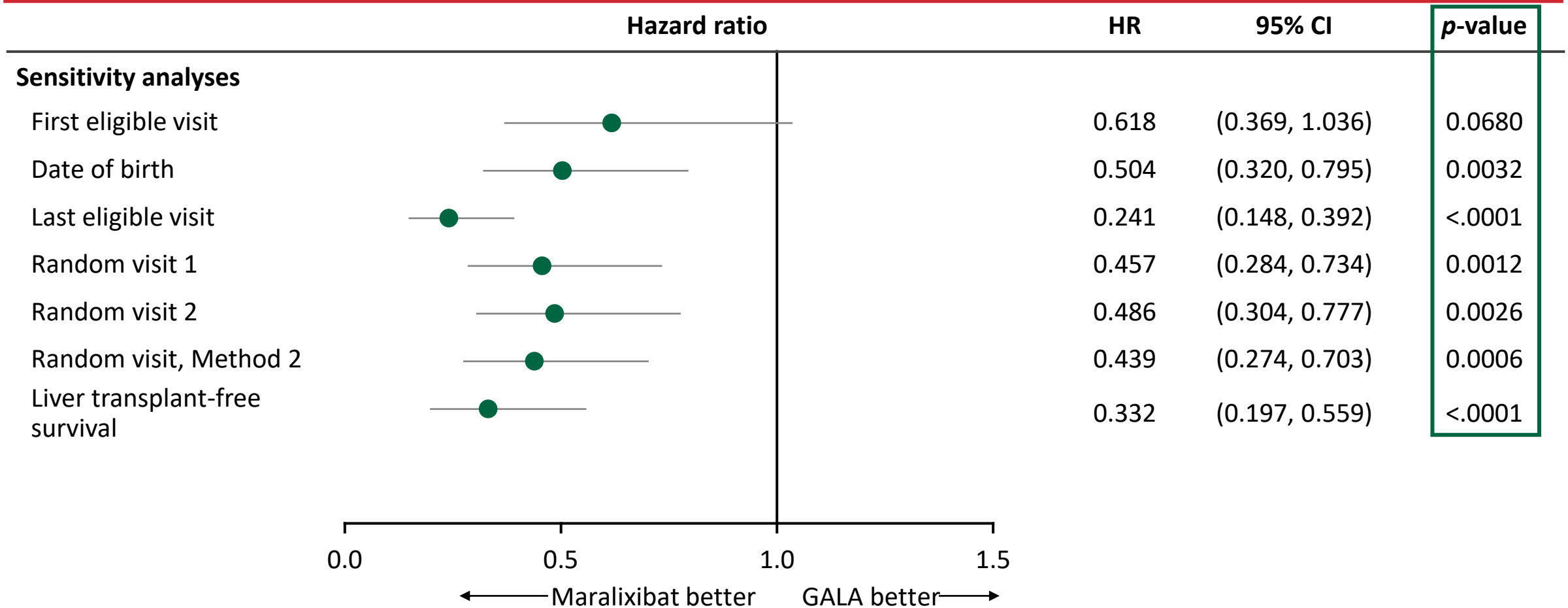


0 yr 1 yr 18 yr  
 Age

- Eligible visit
- Choice of selection of index time

# Consistent results across index times and Liver Transplant Free Survival

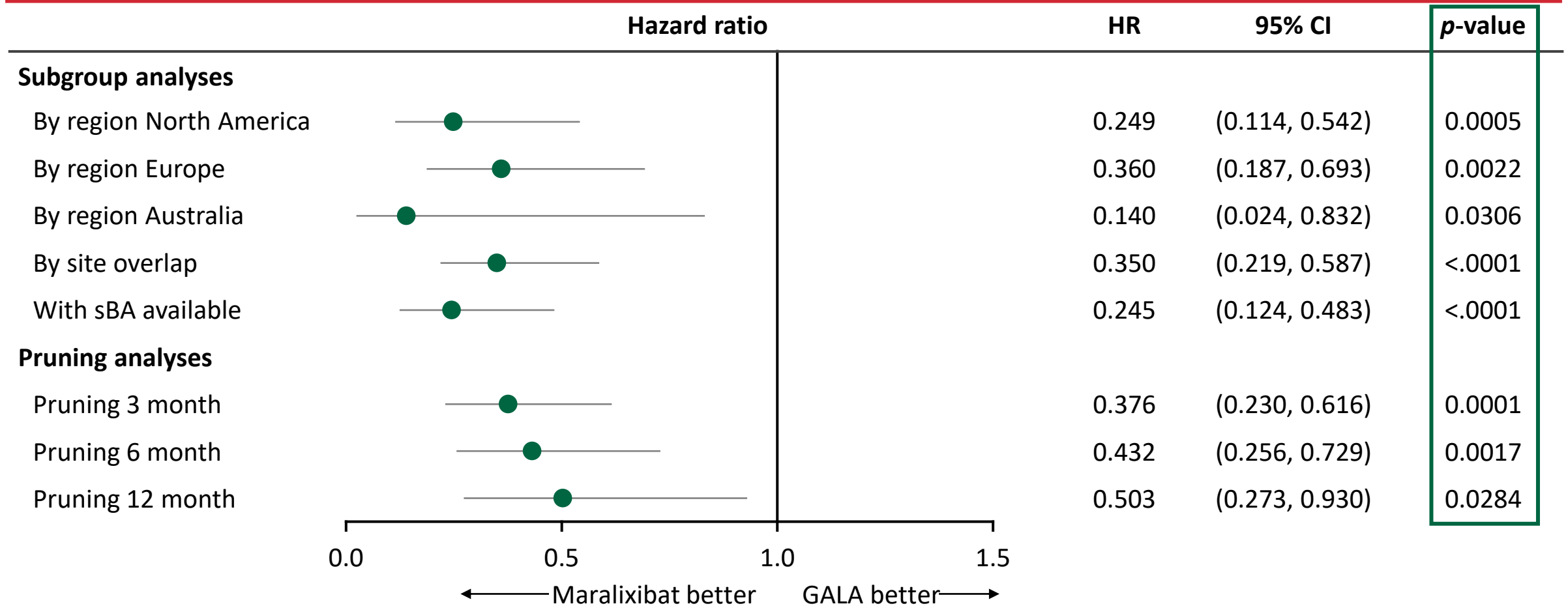
Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control



CI, confidence interval; EFS, event-free survival; HR, hazard ratio.

# Consistent results across sub-group analyses

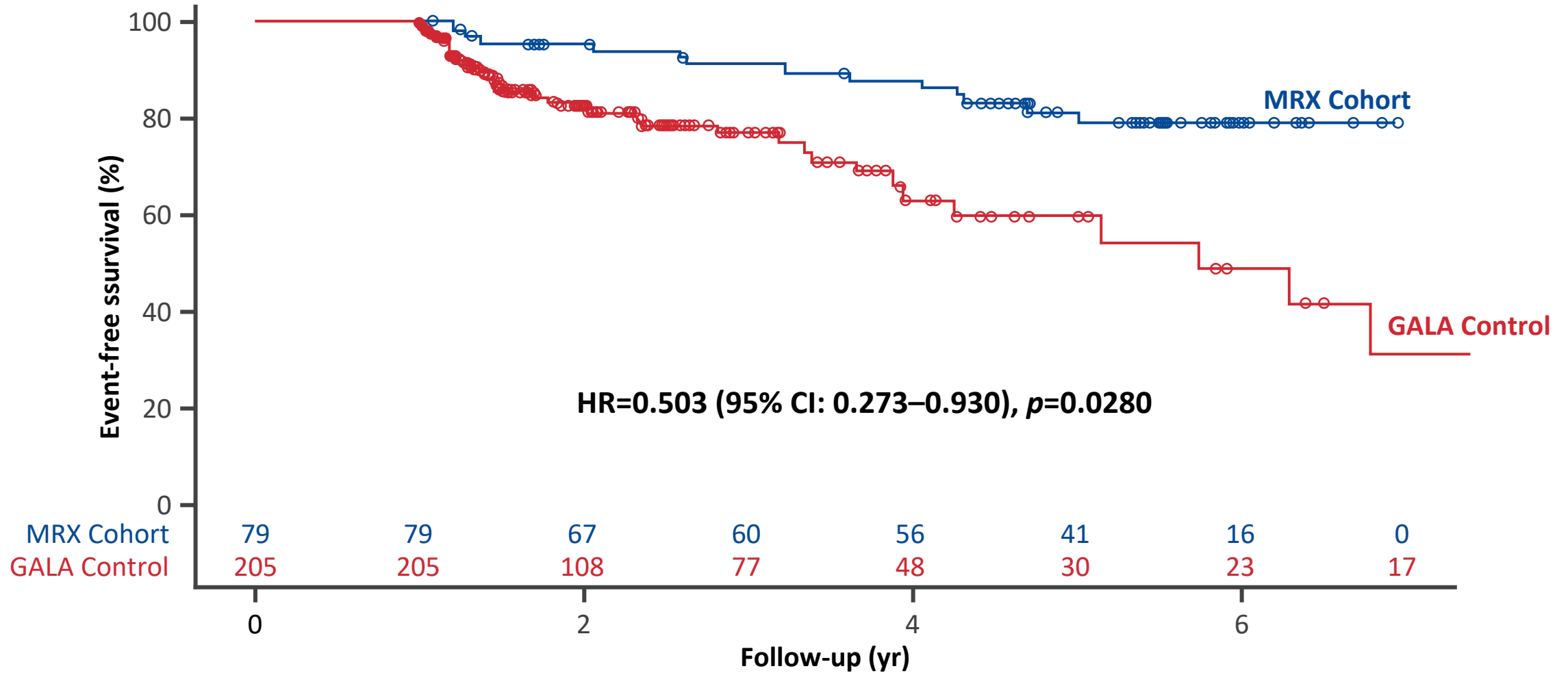
Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control



CI, confidence interval; EFS, event-free survival; HR, hazard ratio; sBA, serum bile acid.

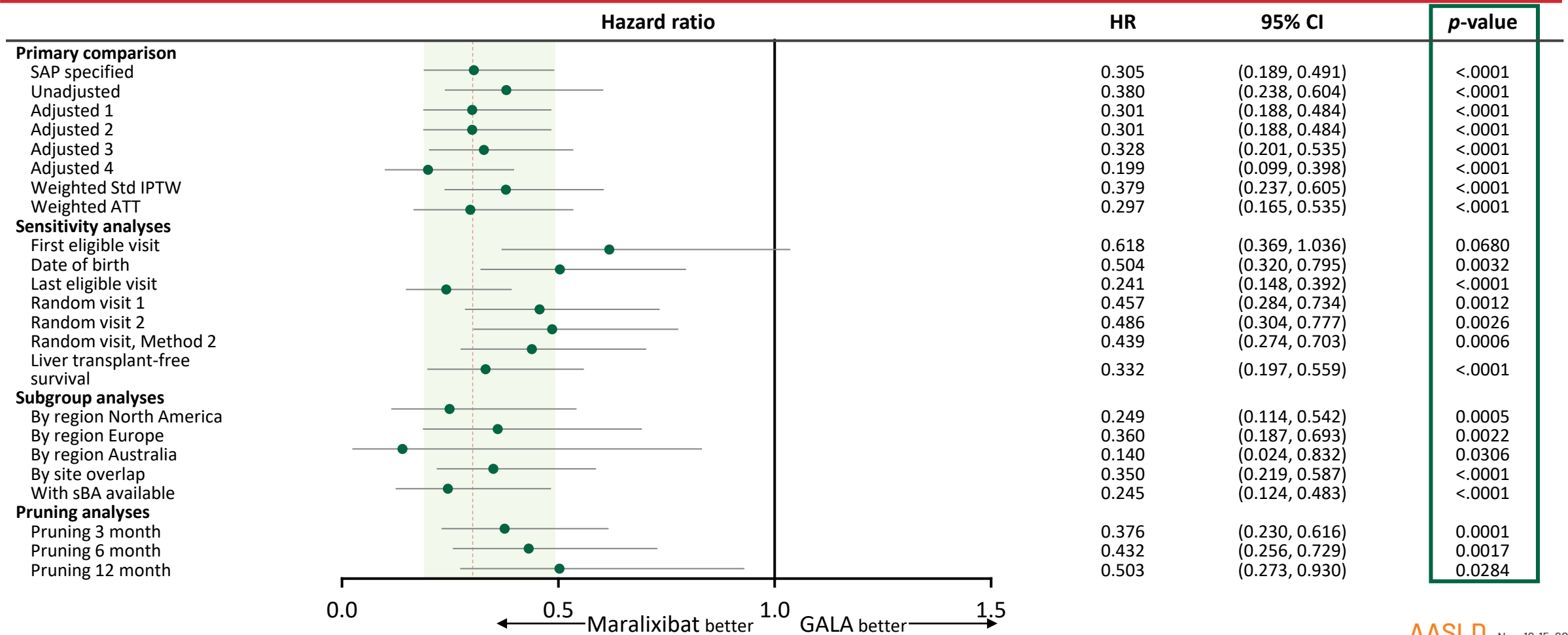
# Maralixibat shows significant improvement in EFS

Pruning for events occurring in the first 12 months



# Consistent results observed across several sensitivity analyses

Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control





# Key takeaway: real-world analytics are difficult but possible

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- This 6-year analysis demonstrates a 70% reduction for clinical outcomes with maralixibat treatment vs natural history in patients with ALGS
- This real-world evidence analysis provides a potential method to evaluate long-term outcomes in interventional studies where placebo comparisons are not feasible
- This type of analysis is possible, particularly where the effect size is dramatic and plausibly linked to the effects of the intervention (eg, maralixibat)
- Consistent findings across multiple sensitivity and sub-group analyses can strengthen the robustness of this approach

# Thank You

**For methodology-related questions:**

Please contact Bettina E. Hansen: [bettina.hansen@utoronto.ca](mailto:bettina.hansen@utoronto.ca)

**For GALA-related questions:**

Please contact Binita M. Kamath: [binita.kamath@sickkids.ca](mailto:binita.kamath@sickkids.ca)