Maralixibat-treated patients with Alagille syndrome (ALGS) demonstrate improved event-free survival in a natural history comparison with patients from the GALA database: Application of real-world evidence analytics

Bettina E. Hansen, PhD[1,2]

and Binita M. Kamath, MBBChir[3] on behalf of The GALA Study Group

[1]Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands
[2]Toronto Center for Liver Disease, University Health Network and the Institute of Health Policy, Management and Evaluation, The University of Toronto, Toronto, Canada
[3]The Hospital for Sick Children and the University of Toronto, Division of Gastroenterology, Hepatology, and Nutrition, Toronto, Canada

Bettina E. Hansen[1,2], Shannon M. Vandriel, Pamela Vig, Will Garner, Li-Ting Li, Huiyu She, Jian-She Wang, Melissa A. Gilbert, Irena Jankowska, Piotr Czubkowski, Dorota Gliwicz-Miedzińska, Emmanuel M. Gonzales, Emmanuel Jacquemin, Jérôme Bouligand, Nancy B. Spinner, Kathleen M. Loomes, David A. Piccoli, Lorenzo D'Antiga, Emanuele Nicastro, Étienne Sokal, Tanguy Demaret, Noelle H. Ebel, Jeffrey A. Feinstein, Rima Fawaz, Silvia Nastasio, Florence Lacaille, Dominique Debray, Henrik Arnell, Björn Fischler, Susan Siew, Michael Stormon, Saul J. Karpen, Rene Romero, Kyung Mo Kim, Woo Yim Baek, Winita Hardikar, Sahana Shankar, Amin J. Roberts, Helen M. Evans, M. Kyle Jensen, Marianne Kavan, Shikha S. Sundaram, Alexander Chaidez, Palaniswamy Karthikeyan, Suzanne Davison, Maria Camila Sanchez, Maria Lorena Cavalieri, Henkjan J. Verkade, Way Seah Lee, James E. Squires, Christina Hajinicolaou, Chatmanee Lertudomphonwanit, Ryan T. Fischer, Catherine Larson-Nath, Yael Mozer-Glassberg, Cigdem Arikan, Henry C. Lin, Jesus Quintero Bernabeu, Seema Alam, Deirdre Kelly, Elisa Carvalho, Cristina Targa Ferreira, Giuseppe Indolfi, Ruben E. Quiros-Tejeira, Pinar Bulut, Pier Luigi Calvo, Zerrin Önal, Pamela L. Valentino, Dev M. Desai, John Eshun, Maria Rogalidou, Antal Dezsőfi, Sabina Wiecek, Gabriella Nebbia, Raquel Borges Pinto, Victorien M. Wolters, María Legarda Tamara, Andréanne N. Zizzo, Jennifer Garcia, Kathleen Schwarz, Marisa Beretta, Thomas Damgaard Sandahl, Carolina Jimemez-Rivera, Nanda Kerkar, Jernej Brecelj, Quais Mujawar, Nathalie Rock, Cristina Molera Busoms, Wikrom Karnsakul, Eberhard Lurz, Ermelinda Santos-Silva, Niviann Blondet, Luis Bujanda, Uzma Shah, Richard J. Thompson, **Binita M. Kamath**[3]

Disclosures

Bettina E. Hansen, PhD

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

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

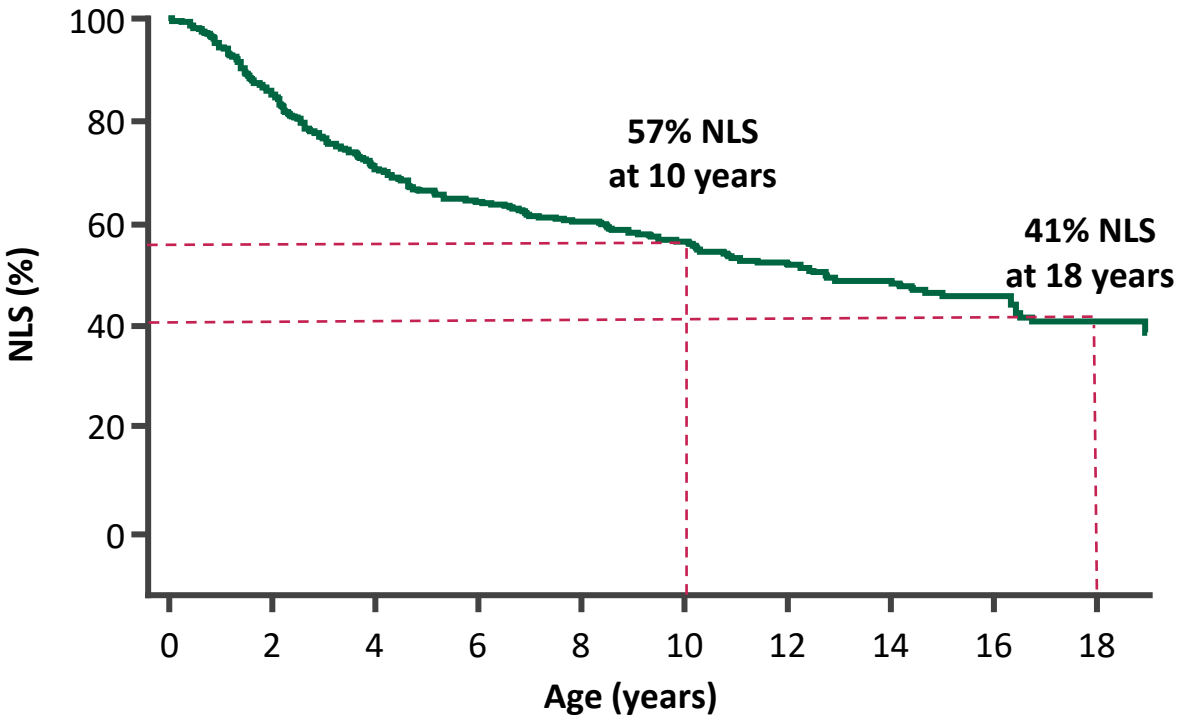
Alagille syndrome: Background

- 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[1,2]

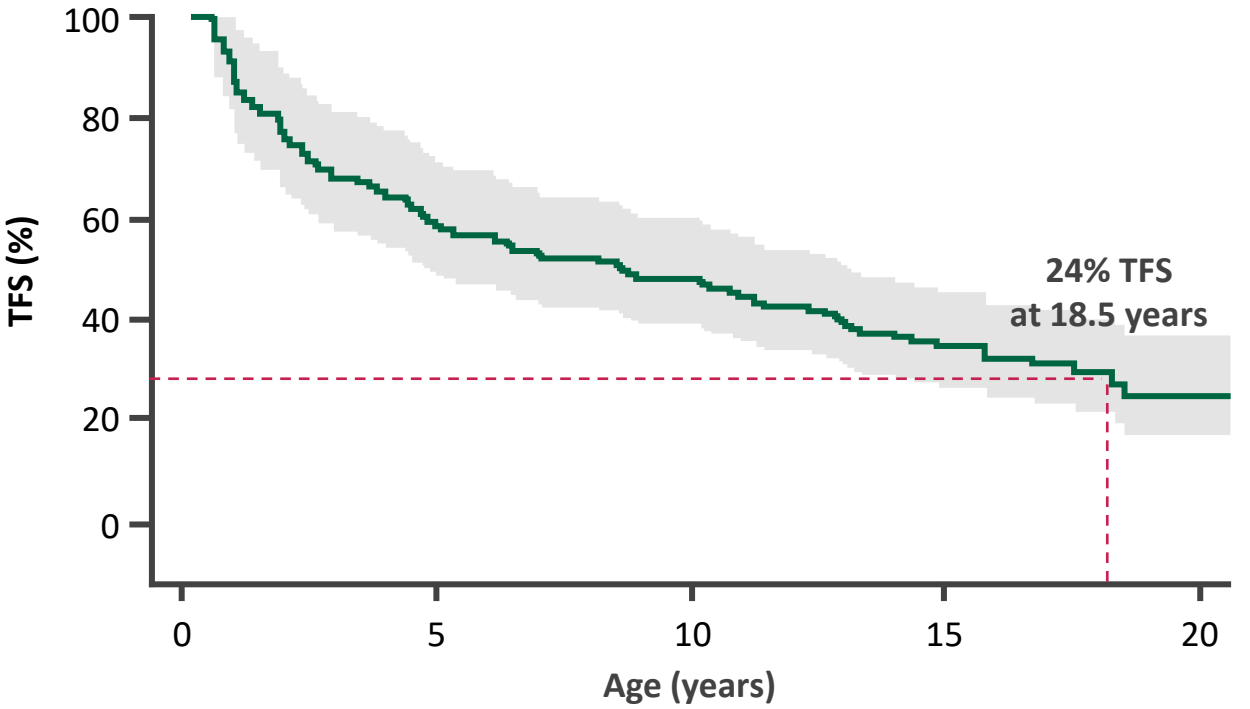
1. Vandriel SM, *et al*. EASL 2020 (poster presentation); 2. Kamath BM, *et al*. *Hepatol Comms* 2020;4:387–398.

Substantial risk for liver transplant in patients with ALGS

GALA[1] (Global)
Native liver survival (NLS) in patients with ALGS presenting with neonatal cholestasis (N = 911)



ChiLDReN (North America network)[2]
Transplant-free survival (TFS) in patients with ALGS (N = 293)

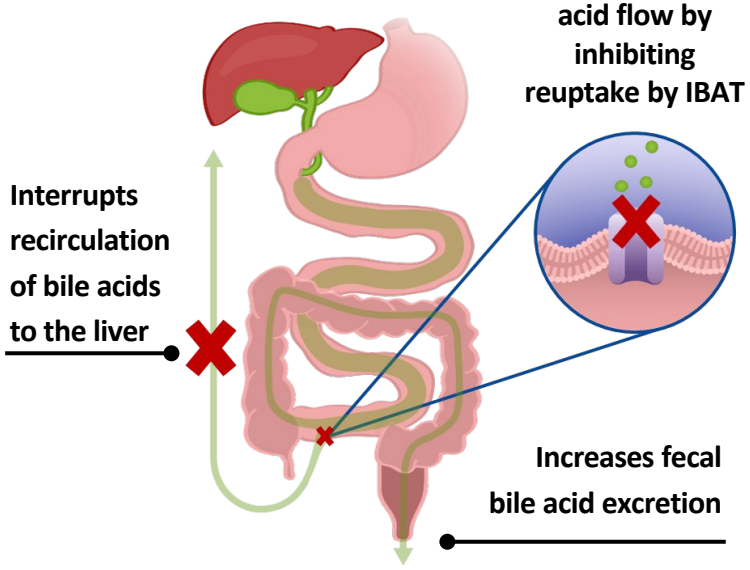


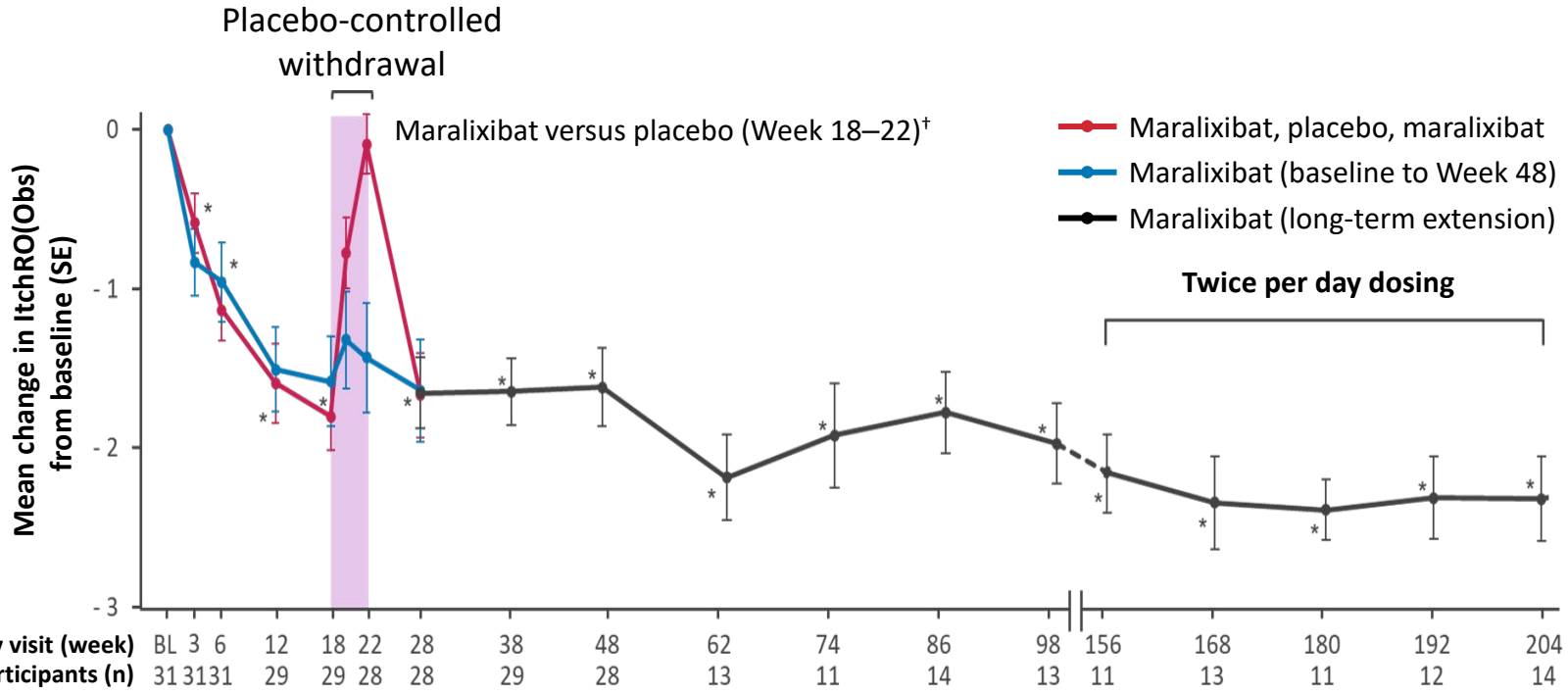
Native Liver Survival = Transplant-Free Survival

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[1,2]

Interrupts recirculation of bile acids to the liver[1]





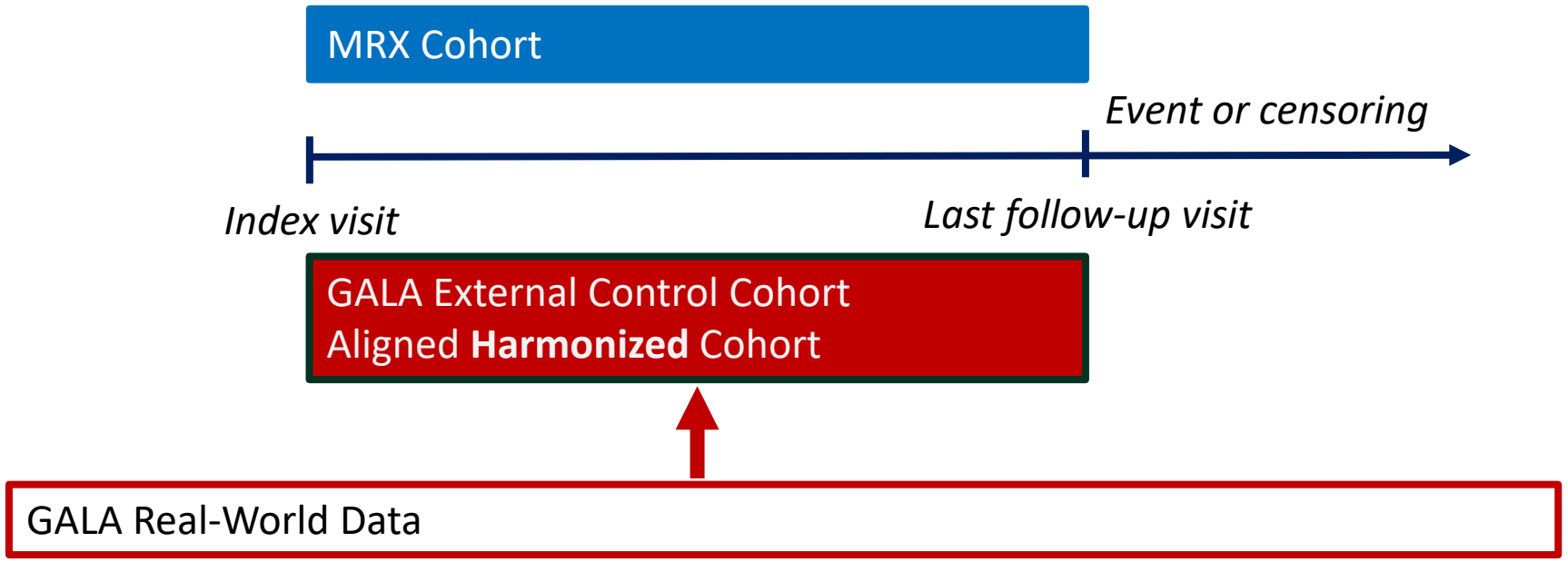
Maralixibat received FDA approval for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older[1,2]

FDA, United States Food and Drug Administration; IBAT(i), ileal bile acid transporter (inhibitor).
*95% CI excludes zero (compared with baseline, overall population); †The maralixibat, placebo, maralixibat treatment group (n = 16) received placebo during the randomized withdrawal period (purple-shaded area), whereas the maralixibat treatment group (n = 13) continued to receive maralixibat.

1. Gonzales E, *et al*. Lancet 2021;398:1581–1592; 2. Mirum Pharmaceuticals, Inc. LIVMARLI® (maralixibat) Prescribing Information. 2021.
Accessed online at: 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

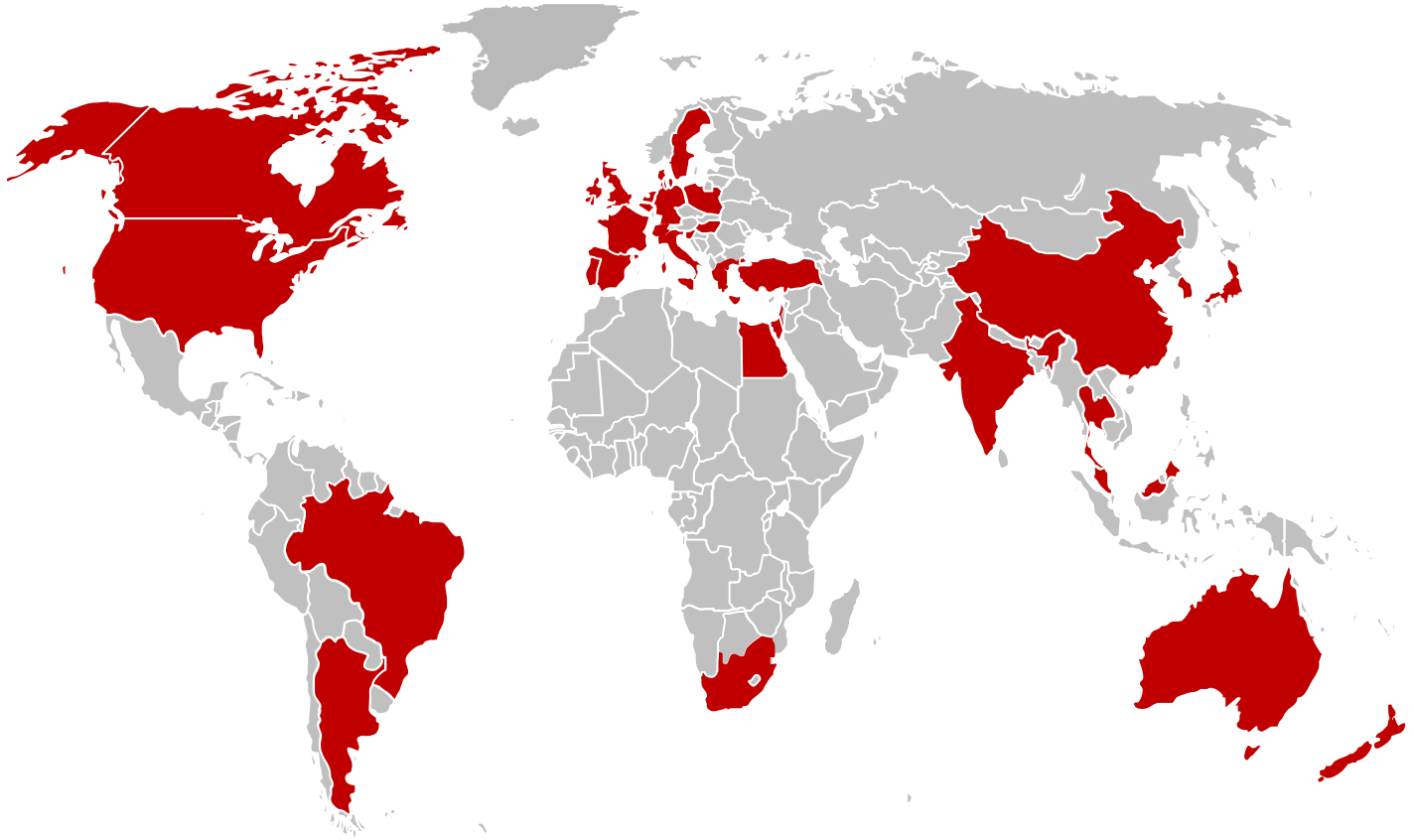
- Use of Real-World Data as a control arm is a potential alternative to assess long-term outcomes. Challenges to overcome include variations in:
  - Baseline characteristics
  - Disease severity and trajectory
  - Background standard of care
  - Inherent bias of participating in a clinical trial

- High bar of standardization and quality of Real-World Data[1]

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 36 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

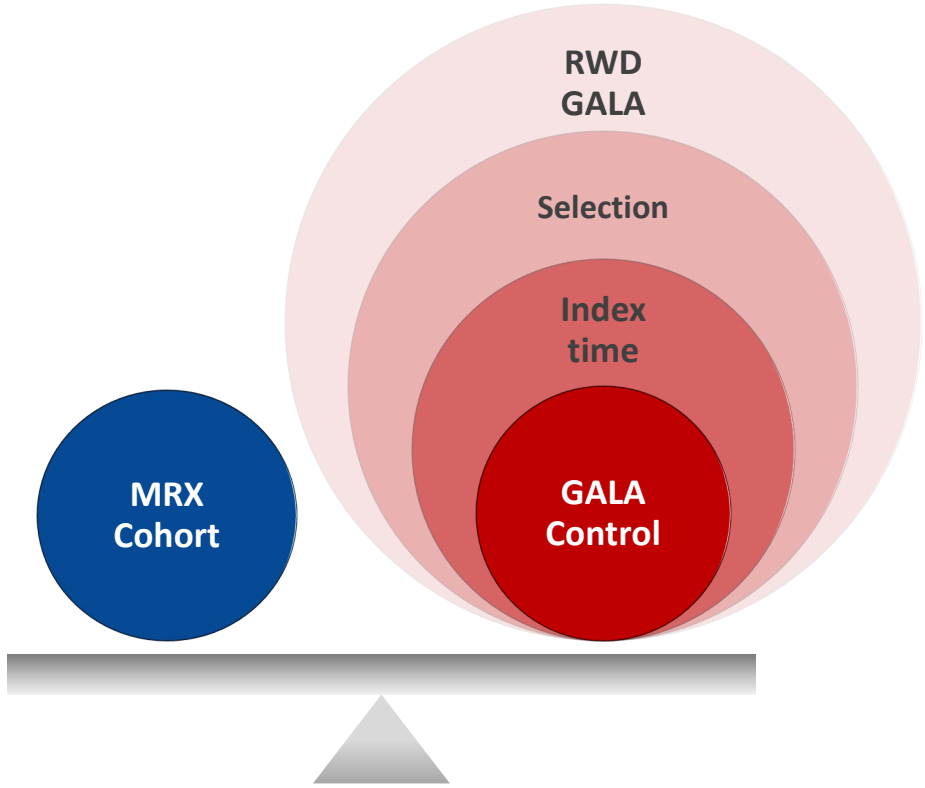
- Align inclusion / exclusion criteria
- Overlay sites / regions / calendar time

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



ATT, average treatment effect in the treated; IPTW, inverse probability of treatment weights.

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: ≥1 year and <18 years
- Diagnosed after 1990
- Cholestasis, defined by one or more of the following:
  - Total sBA >3 x ULN
  - Conjugated or direct bilirubin >1 mg/dL
  - Total bilirubin >2 mg/dL
  - GGT >3 x ULN

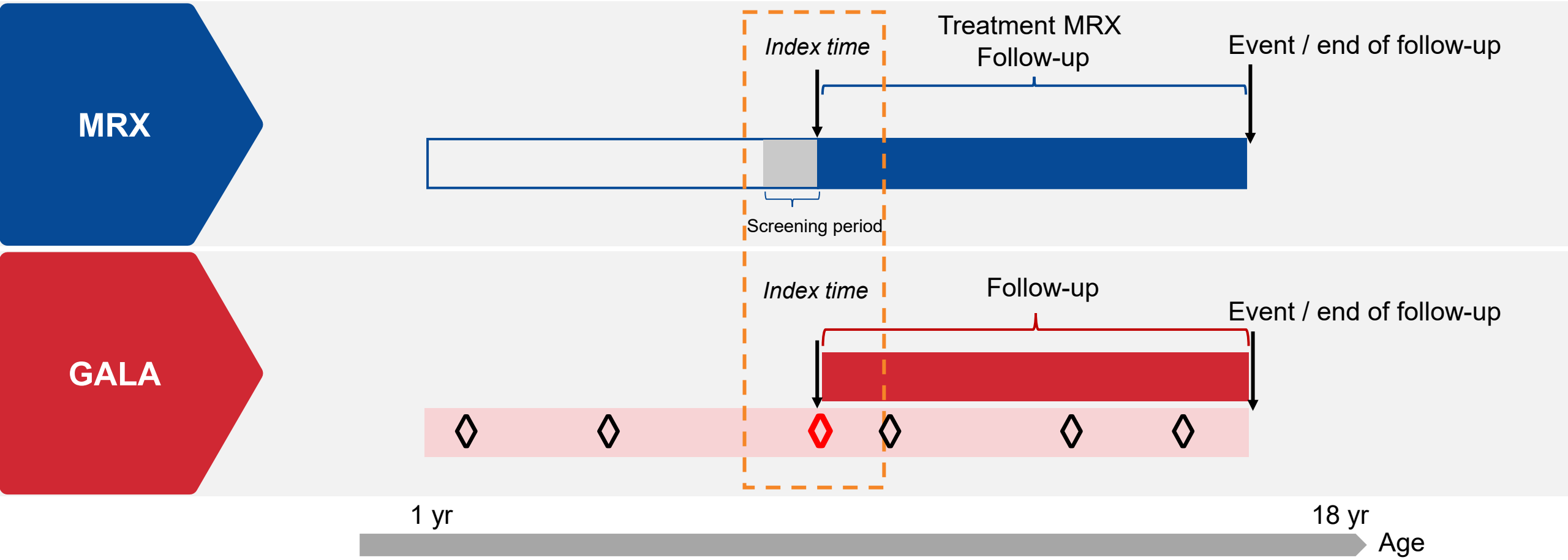
Key Exclusion Criteria

- ALT >15 x 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

ALT, alanine aminotransferase; BD, biliary diversion; GGT, gamma-glutamyl transferase; sBA, serum bile acid; ULN, upper limit of normal.
Maralixibat ALGS Studies 301, 302 and 304 and extensions.

Selection of index time: Best fit



◊ Eligible visit

◊ Eligible visit and selection of index time

MRX, maralixibat.

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 (%)	***JAG1***	81 (97.6)	330 (95.1)	0.55
	NOTCH2	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

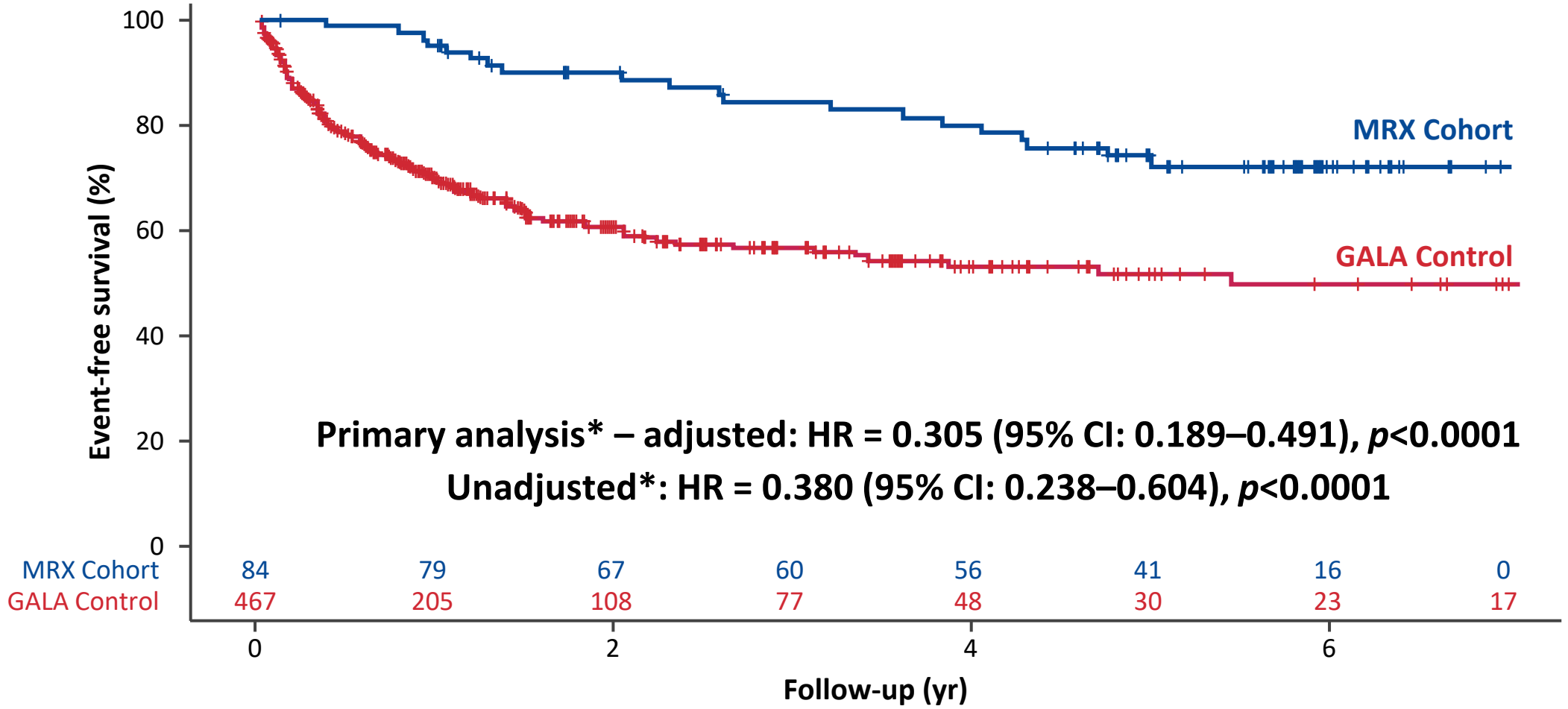
Baseline characteristic		MRX Cohort N = 84	GALA Control N = 469	*p*-value
Total bilirubin, mg/dL	Median (Q1,Q3)	3.15 (1.00, 8.15)	1.99 (0.60, 11.52)	0.392
	<2 mg/dL	37 (44.0)	235 (50.1)	0.306
	≥2 mg/dL	47 (56.0)	234 (49.9)	
GGT*, U/L	Median (Q1, Q3), log_{10} x ULN	1.25 (0.93, 1.44)	1.24 (0.93, 1.52)	0.582
	<3 x ULN	3 (3.6)	6 (1.3)	0.143
	≥3 x 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

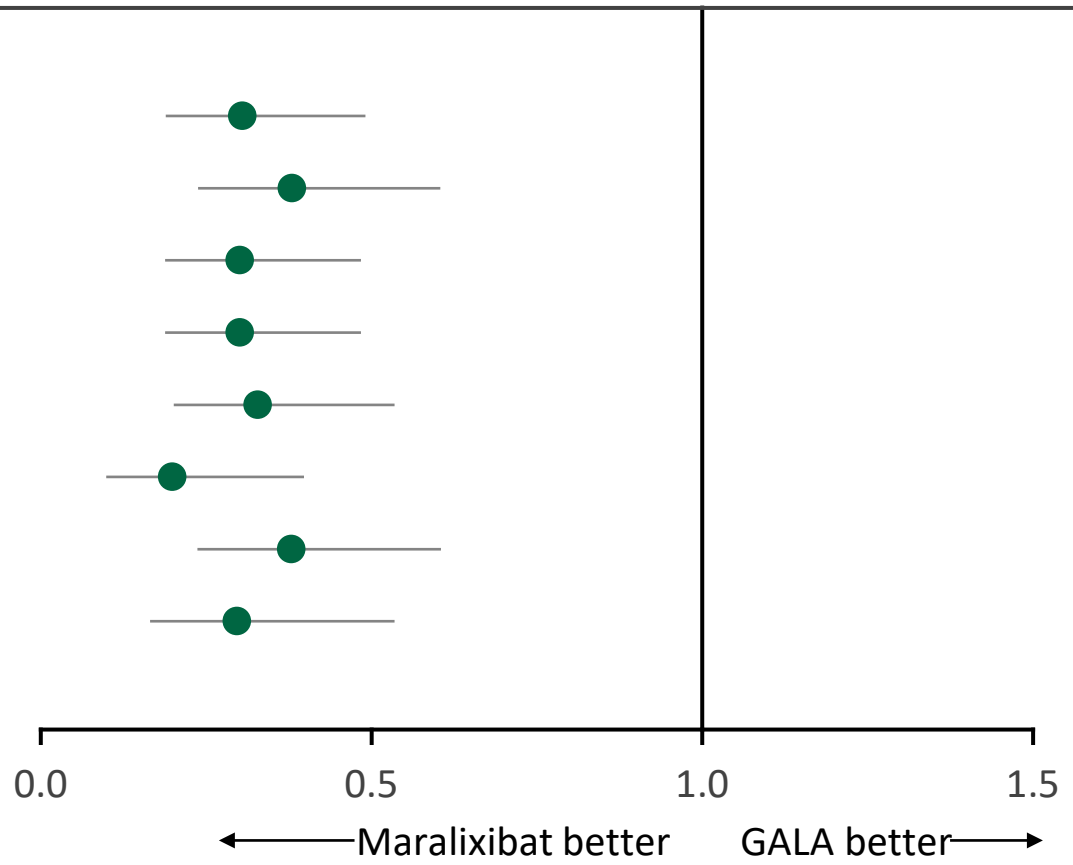
EFS: biliary diversion surgery, decompensation event, liver transplantation, or death



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

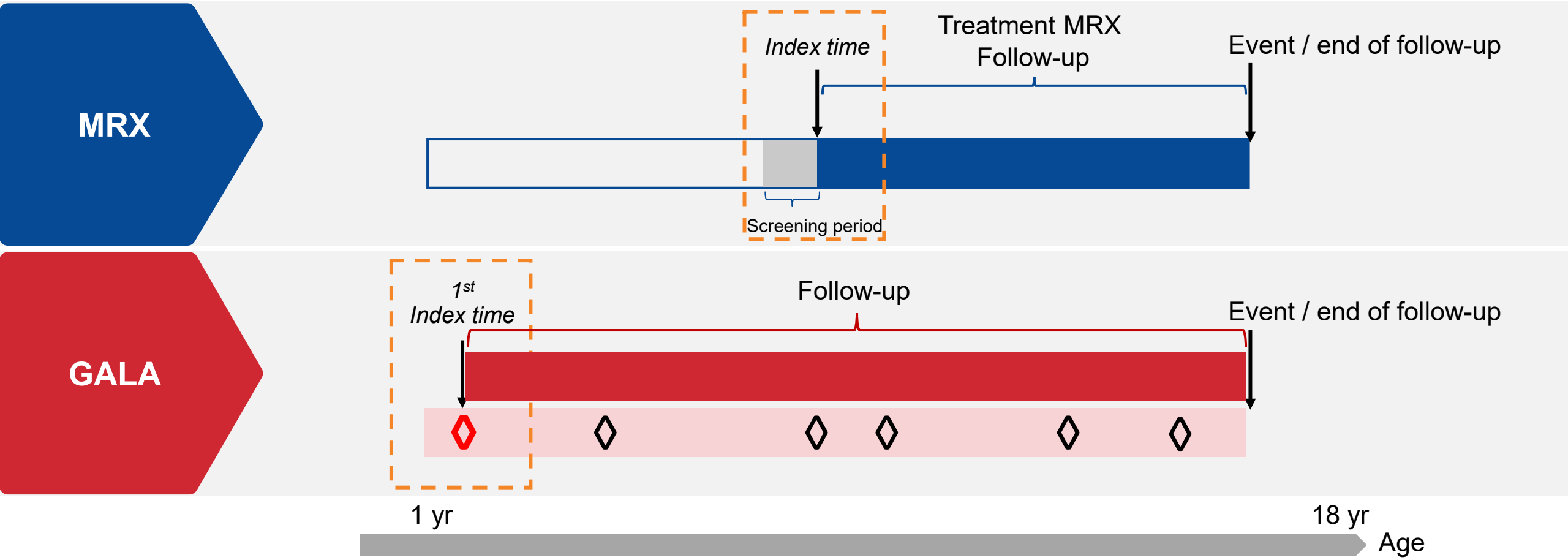
Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control



	HR	95% CI	*p*-value
Primary comparison			
SAP specified	0.305	(0.189, 0.491)	<.0001
Unadjusted	0.380	(0.238, 0.604)	<.0001
Adjusted 1	0.301	(0.188, 0.484)	<.0001
Adjusted 2	0.301	(0.188, 0.484)	<.0001
Adjusted 3	0.328	(0.201, 0.535)	<.0001
Adjusted 4	0.199	(0.099, 0.398)	<.0001
Weighted Std IPTW	0.379	(0.237, 0.605)	<.0001
Weighted ATT	0.297	(0.165, 0.535)	<.0001

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

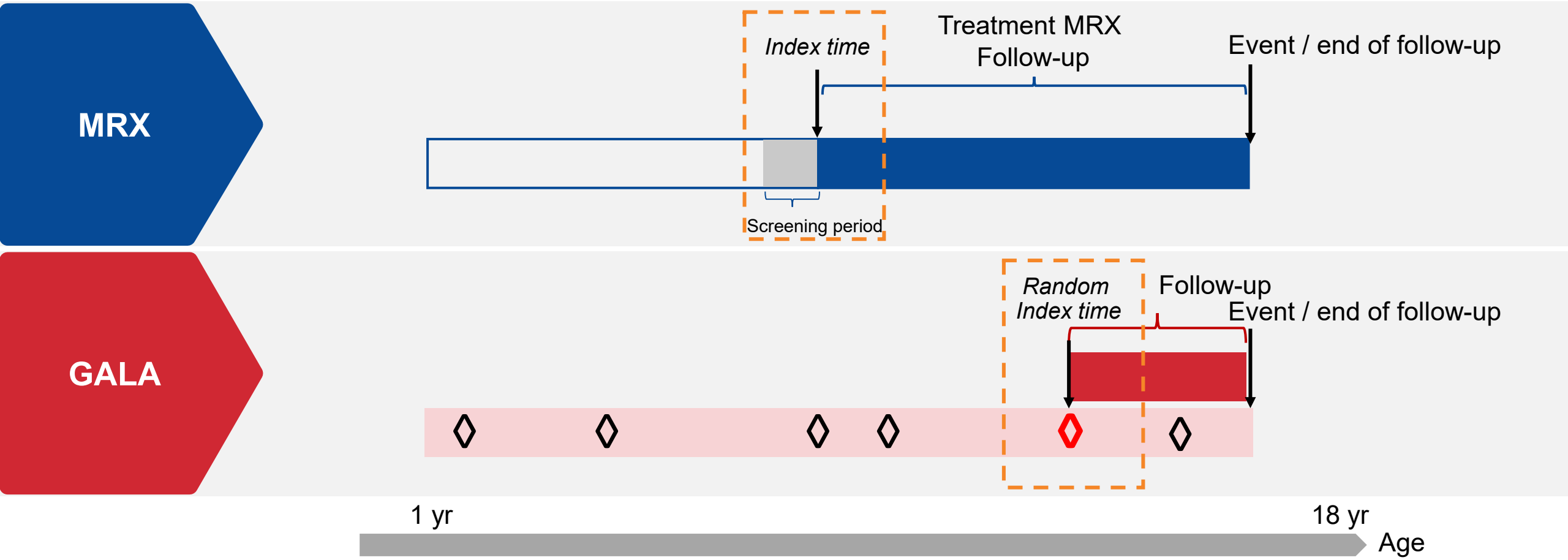


◊ Eligible visit

◊ Eligible visit and selection of index time

MRX, maralixibat.

Selection of index time: Random visit

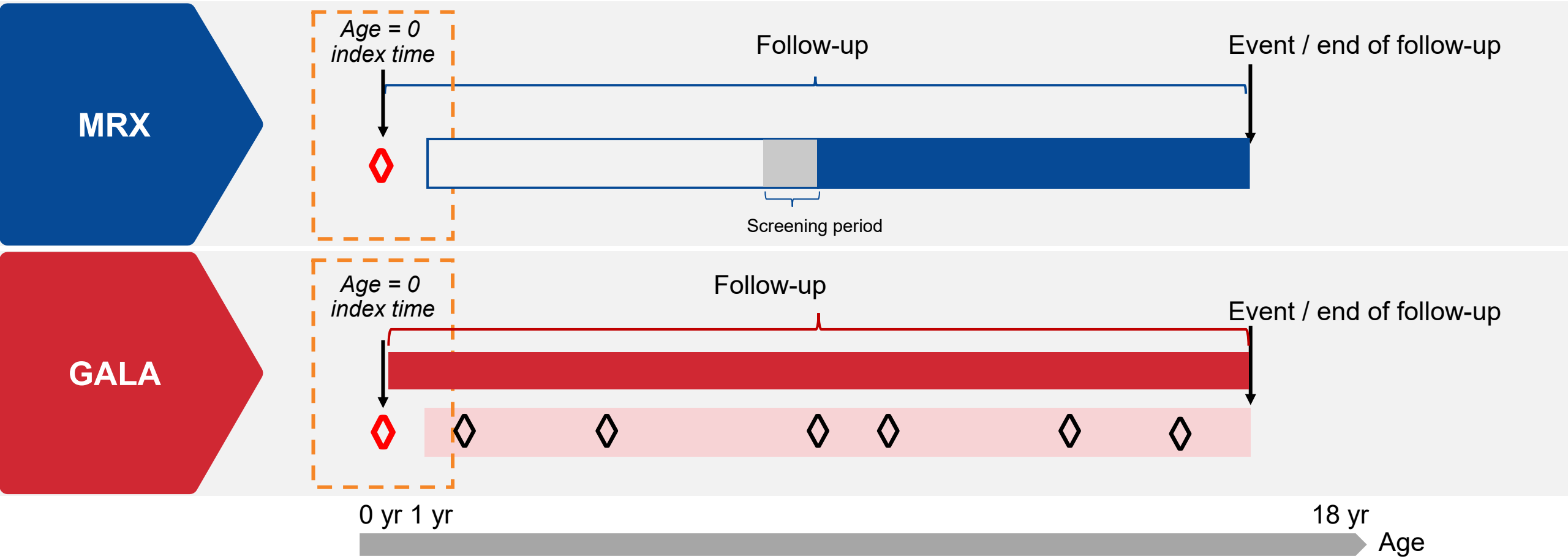


◊ Eligible visit

◊ Eligible visit and selection of index time

MRX, maralixibat.

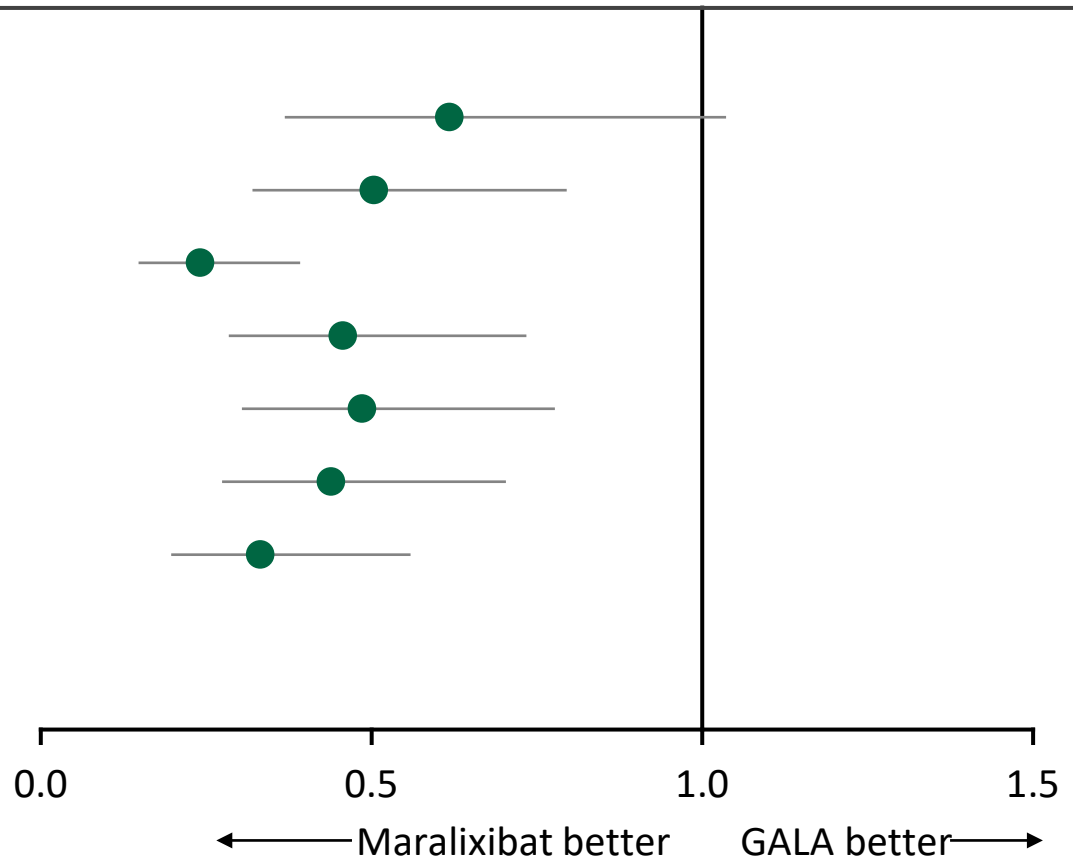
Selection of index time: Date of birth



MRX, maralixibat.

Consistent results across index times and liver transplant-free survival

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

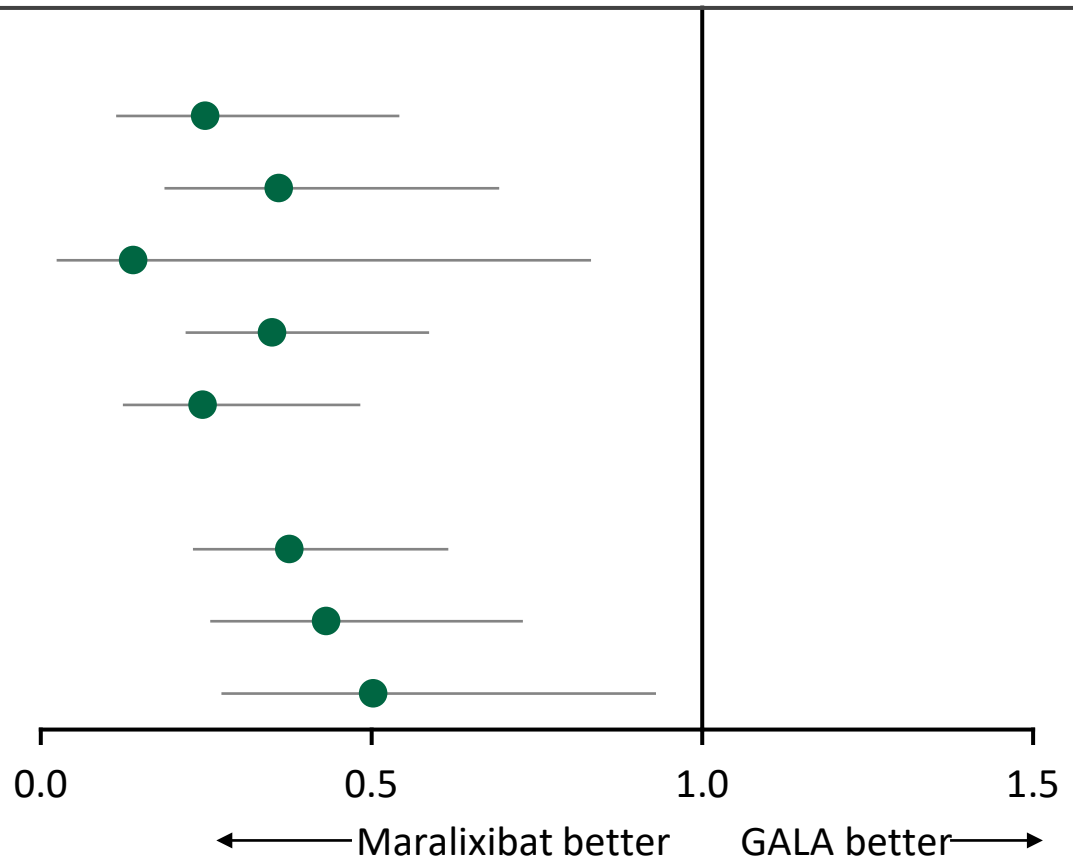


	HR	95% CI	*p*-value
Sensitivity analyses			
First eligible visit	0.618	(0.369, 1.036)	0.0680
Date of birth	0.504	(0.320, 0.795)	0.0032
Last eligible visit	0.241	(0.148, 0.392)	<.0001
Random visit 1	0.457	(0.284, 0.734)	0.0012
Random visit 2	0.486	(0.304, 0.777)	0.0026
Random visit, Method 2	0.439	(0.274, 0.703)	0.0006
Liver transplant-free survival	0.332	(0.197, 0.559)	<.0001

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

Consistent results across subgroup analyses

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

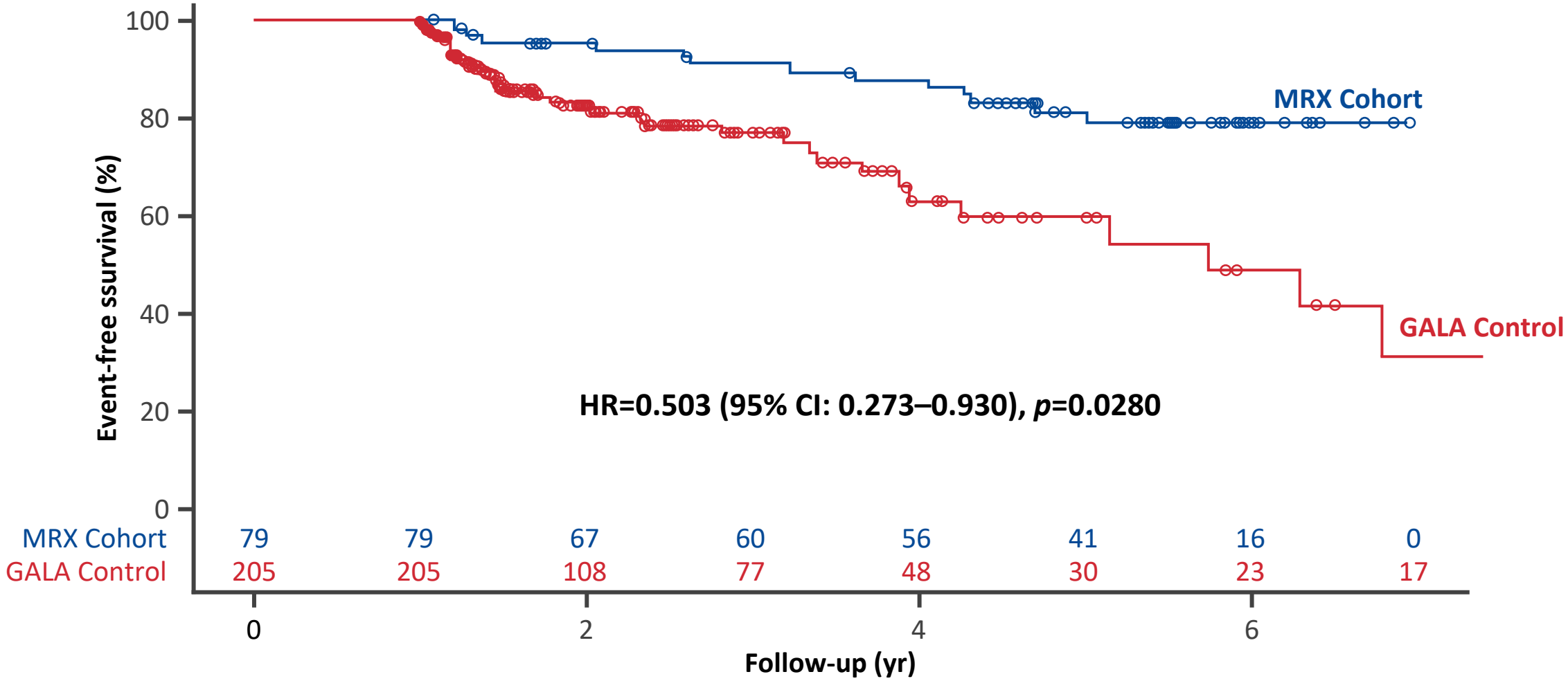


	Hazard ratio	HR	95% CI	*p*-value
Subgroup analyses				
By region North America		0.249	(0.114, 0.542)	0.0005
By region Europe		0.360	(0.187, 0.693)	0.0022
By region Australia		0.140	(0.024, 0.832)	0.0306
By site overlap		0.350	(0.219, 0.587)	<.0001
With sBA available		0.245	(0.124, 0.483)	<.0001
Pruning analyses				
Pruning 3 month		0.376	(0.230, 0.616)	0.0001
Pruning 6 month		0.432	(0.256, 0.729)	0.0017
Pruning 12 month		0.503	(0.273, 0.930)	0.0284

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

Maralixibat shows significant improvement in EFS

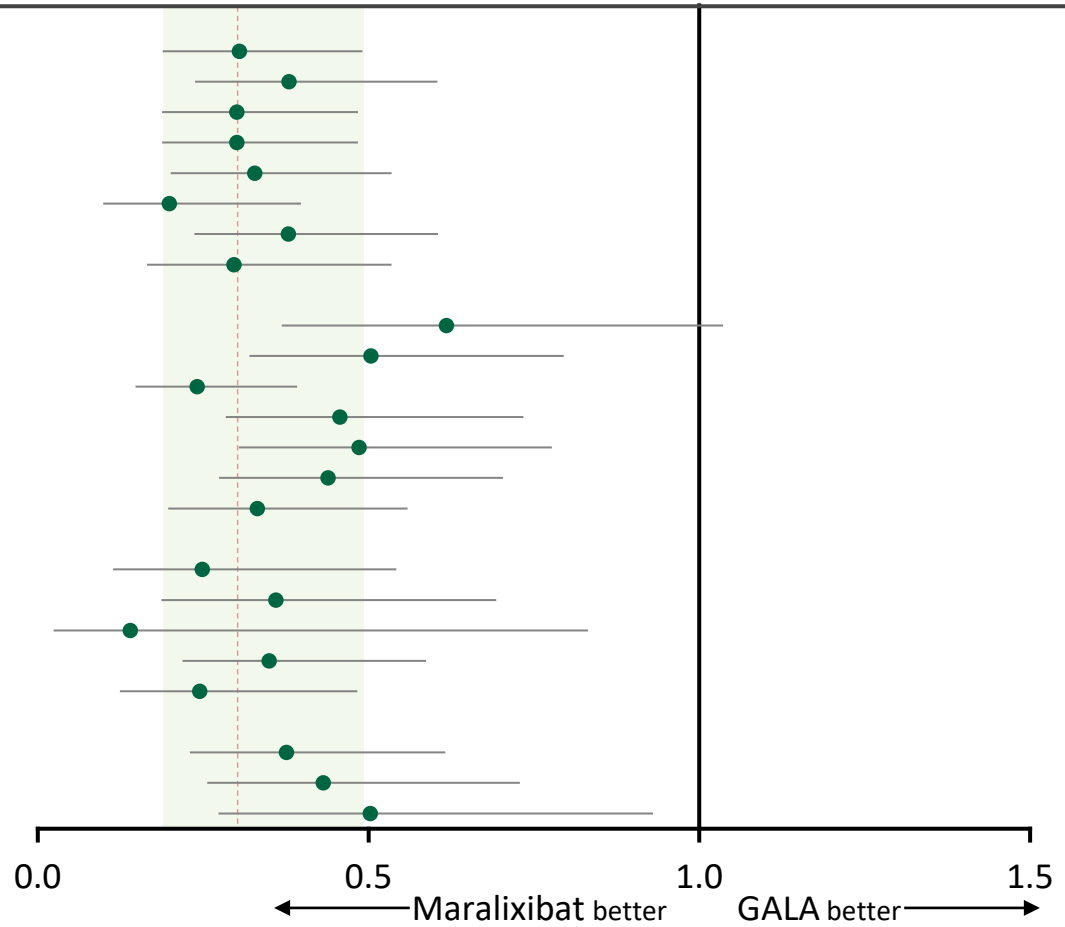
Pruning for events occurring in the first 12 months



CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat.

Consistent results observed across several sensitivity analyses

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



	HR	95% CI	*p*-value
Primary comparison			
SAP specified	0.305	(0.189, 0.491)	<.0001
Unadjusted	0.380	(0.238, 0.604)	<.0001
Adjusted 1	0.301	(0.188, 0.484)	<.0001
Adjusted 2	0.301	(0.188, 0.484)	<.0001
Adjusted 3	0.328	(0.201, 0.535)	<.0001
Adjusted 4	0.199	(0.099, 0.398)	<.0001
Weighted Std IPTW	0.379	(0.237, 0.605)	<.0001
Weighted ATT	0.297	(0.165, 0.535)	<.0001
Sensitivity analyses			
First eligible visit	0.618	(0.369, 1.036)	0.0680
Date of birth	0.504	(0.320, 0.795)	0.0032
Last eligible visit	0.241	(0.148, 0.392)	<.0001
Random visit 1	0.457	(0.284, 0.734)	0.0012
Random visit 2	0.486	(0.304, 0.777)	0.0026
Random visit, Method 2	0.439	(0.274, 0.703)	0.0006
Liver transplant-free survival	0.332	(0.197, 0.559)	<.0001
Subgroup analyses			
By region North America	0.249	(0.114, 0.542)	0.0005
By region Europe	0.360	(0.187, 0.693)	0.0022
By region Australia	0.140	(0.024, 0.832)	0.0306
By site overlap	0.350	(0.219, 0.587)	<.0001
With sBA available	0.245	(0.124, 0.483)	<.0001
Pruning analyses			
Pruning 3 month	0.376	(0.230, 0.616)	0.0001
Pruning 6 month	0.432	(0.256, 0.729)	0.0017
Pruning 12 month	0.503	(0.273, 0.930)	0.0284

Key takeaway: Real-world analytics are difficult but possible

- 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 (e.g. maralixibat)
- Consistent findings across multiple sensitivity and subgroup analyses can strengthen the robustness of this approach

Thank You

For methodology-related questions:

Please contact Bettina E. Hansen: b.hansen@erasmusmc.nl

For GALA-related questions:

Please contact Binita M. Kamath: binita.kamath@sickkids.ca