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

Hansen BE, Vandriel SM, Vig P, Garner W, Mogul D, Loomes KM, Piccoli DA, Rand EB, Jankowska I, Czubkowski P, Gliwicz-Miedzińska D, Gonzales EM, Jacquemin E, Bouligand J, D'Antiga L, Nicastro E, Arnell H, Fischler B, Sokal E, Demaret T, Siew S, Stormon M, Karpen SJ, Romero R, Ebel NH, Feinstein JA, Roberts AJ, Evans HM, Sundaram SS, Chaidez A, Hardikar W, Shankar S, Fischer RT, Lacaille F, Debray D, Lin HC, Jensen MK, Jaramillo C, Karthikeyan P, Davison S, Indolfi G, Verkade HJ, Larson-Nath C, Quiros-Tejeira RE, Valentino PL, Rogalidou M, Dezsőfi A, Squires JE, Schwarz K, Calvo PL, Quintero Bernabeu J, Zizzo AN, Nebbia G, Bulut P, Santos-Silva E, Fawaz R, Nastasio S, Karnsakul W, Legarda Tamara M, Molera Bussoms C, Kelly D, Damgaard Sandahl T, Jimenez-Rivera C, Banales JM, Mujawar Q, Li LT, She H, Wang JS, Kim KM, Baek WY, Sanchez MC, Cavalieri ML, Lee WS, Hajinicolaou C, Lertudomphonwanit C, Waisbourd-Zinman O, Arikan C, Alam S, Carvalho E, Melere M, Eshun J, Önal Z, Desai DM, Wiecek S, Borges Pinto R, Wolters VM, Garcia J, Beretta M, Kerkar N, Brecelj J, Rock N, Lurz E, Blondet N, Shah U, Thompson RJ, **Kamath BM**,[1] and The Global ALagille Alliance (GALA) Study Group

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BACKGROUND

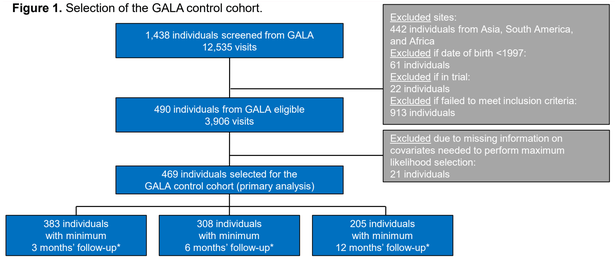
- Alagille syndrome (ALGS) is a rare, autosomal-dominant multisystem disorder dominated by cholestatic liver disease with bile duct paucity, leading to retained hepatic bile acids resulting in cholestasis, in association with an array of other clinical features that are variably expressed.[1]
- Key clinical features in those with hepatic involvement are severe debilitating pruritus, growth failure, and xanthomas, which are the leading indications for liver transplantation.[1–3]
- Transplant-free survival in children with ALGS is 24–40% at 18.5 years of age.[3,4]
- Global ALagille Alliance (GALA) is an international natural history clinical database that contains retrospective data for clinical parameters, biochemistries, and outcomes from more than 1,400 children with ALGS from 29 countries (as per this analysis' cutoff date).[3]
- Maralixibat (MRX) is an ileal bile acid transporter inhibitor (IBATi) that interrupts enterohepatic bile acid recirculation and reduces serum bile acid (sBA) levels.[5] MRX is the first US Food and Drug Administration (FDA) approved treatment for cholestatic pruritus in patients with ALGS 1 year of age and older.[5,6]

AIM

- To compare time to first clinical event between an MRX cohort of 84 patients treated for up to 6 years and an external control cohort from the GALA database.
- Events were defined as liver transplantation, biliary diversion surgery, a decompensation event (ascites requiring therapy or varices requiring intervention at endoscopy), or death.

METHODS

Figure 1. Selection of the GALA control cohort.



*A minimum amount of follow-up time was considered in order to avoid immortal time bias (that is, an early observed effect due to survivor treatment selection bias).
GALA, Global ALagille Alliance.

Selection process:

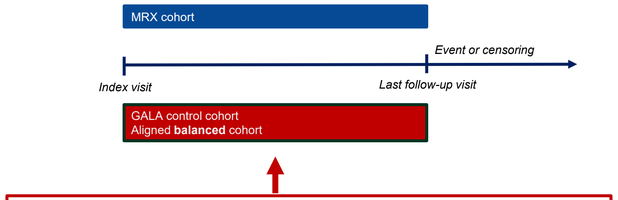
- The statistician was blinded to clinical outcomes per the prespecified statistical analysis plan during the selection of patients and index time.
- Key inclusion criteria included: age at inclusion ≥12 months and <18 years; diagnosed after 1990; cholestasis defined by one or more of: total sBA >3 times the upper limit of normal, conjugated or direct bilirubin >1 mg/dL, total bilirubin >2 mg/dL, or gamma-glutamyl transferase >3 times the upper limit of normal; and residence in North America, Europe, or Australia, where the MRX trials were conducted.
- Index time and balance assessment:
  - The selected index time for the MRX cohort was when patients started receiving the drug.
  - For the GALA control cohort, multiple index times were considered as patients may fulfill eligibility criteria at multiple time points. The 'primary' index time was selected based on the maximum likelihood approach of identifying the best fit (Figure 3) with respect to the prespecified covariates: age, sex, total bilirubin, and alanine transaminase.
  - Balance of baseline variables between the MRX and the selected GALA control cohorts were assessed and weighting was performed if required. Weights were estimated by propensity score methods.

Time-to-event analysis:

- Time-to-event analyses were performed using Kaplan–Meier and Cox regression models, and multiple sensitivity analyses were explored, including:
  - Adjustments for different covariates (e.g. alanine transaminase, bilirubin, gamma-glutamyl transferase, sBA).
  - Sensitivity analyses were performed to determine the robustness of the findings (i.e. different index times, transplant-free survival, pruning events, standardized inverse probability of treatment weights, and average treatment effect in the treated for weighting).
  - Pruning – elimination of events immediately following the index time – was performed to minimize immortal time bias.
  - Regions and overlapping sites – to control for regional standard of care and overlapping centers that participated in both the MRX studies and GALA.

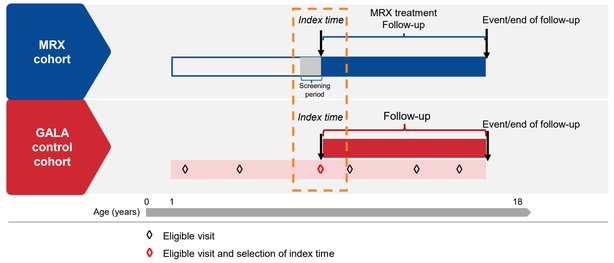
METHODS

Figure 2. Study design.



GALA, Global ALagille Alliance; MRX, maralixibat.

Figure 3. Selection of index time: Best fit.



GALA, Global ALagille Alliance; MRX, maralixibat.

Baseline characteristics were well balanced between the MRX and GALA control cohorts

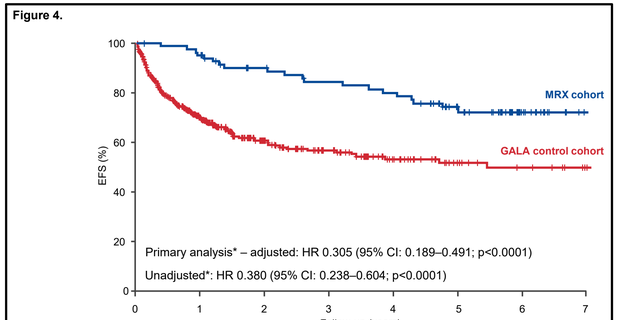
Baseline characteristic		MRX cohort n = 84	GALA control cohort n = 469	p value
Sex, n (%)	Male	49 (58.3)	274 (58.4)	0.988
	Female	35 (41.7)	195 (41.6)	
Age at BL, years	Median (Q1–Q3)	5.6 (2.7–9.9)	4.3 (2.2–9.6)	0.078
Year of birth	Median (Q1–Q3)	2009 (2005–2012)	2009 (2004–2013)	0.249
Region, n (%)	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 (%)	*JAGGED1*	81 (97.6)	330 (95.1)	0.55*
	NOTCH2	2 (2.4)	17 (4.9)	
	Other / unknown	1 (0.2)	37 (9.6)	
sBA†, µmol/L	Median (Q1–Q3)	200 (81–371) (*100% measured*)	125 (39–260) (*15% measured*)	0.003

*Due to >20% of the cells having expected counts <5, chi-square results may be invalid, and Fisher's exact test was used instead.
†Approximately 85% of the sBA values were not available in the GALA database as frequent sBA measurement is not part of clinical practice. Baseline sBA data were available for 73 GALA patients.
BL, baseline; GALA, Global ALagille Alliance; MRX, maralixibat; Q1, first quartile; Q3, third quartile; sBA, serum bile acid.

RESULTS

MRX shows a 70% improvement in event-free survival (EFS) compared with natural history controls

Figure 4.



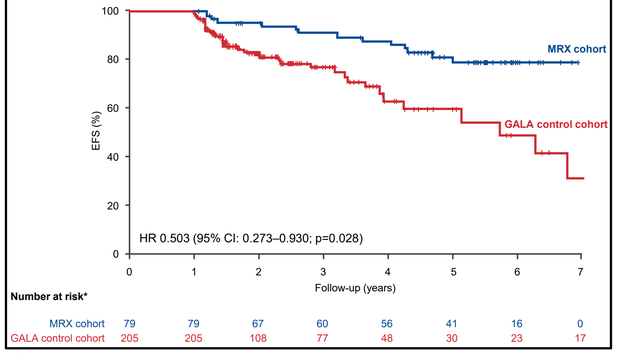
Number at risk†

MRX cohort	84	79	67	60	56	41	16	0
GALA control cohort	467	205	108	77	48	30	23	17

*Cox regression models for the primary analysis: primary prespecified (adjusted), where the effect of MRX vs. GALA log likelihood test was adjusted for age, sex, bilirubin, and ALT (according to the statistical analysis plan), and primary unadjusted.
†The number at risk is the original number of participants (at time 0) minus those who had an event or were censored (e.g. lost to follow-up) prior to the start of the given period.
ALT, alanine transaminase; CI, confidence interval; EFS, event-free survival; GALA, Global ALagille Alliance; HR, hazard ratio; MRX, maralixibat.

MRX shows significant improvement in EFS after pruning for events occurring in the first 12 months

Figure 5.



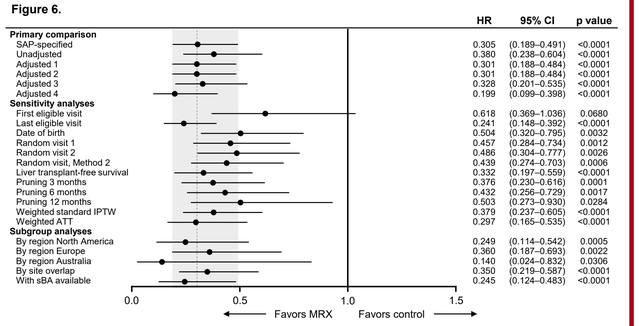
Number at risk*

MRX cohort	79	79	67	60	56	41	16	0
GALA control cohort	205	205	108	77	48	30	23	17

*The number at risk is the original number of participants (at time 0) minus those who had an event or were censored (e.g. lost to follow-up) prior to the start of the given period. Participants who had events within the first 12 months were excluded from the analysis (thus there are no events within the first year). This was performed in an effort to avoid immortal time bias.
CI, confidence interval; EFS, event-free survival; GALA, Global ALagille Alliance; HR, hazard ratio; MRX, maralixibat.

Consistent evidence of improved EFS seen across sensitivity and subgroup analyses

Figure 6.



Sensitivity analyses for the primary comparison included: SAP-specified analyses (Cox-regression model adjusted for age, sex, total bilirubin, and ALT); Unadjusted (only the covariate being treatment was performed [EFS]); Adjusted 1 (Cox-regression model adjusted for age, total bilirubin, and GGT); Adjusted 2 (Cox-regression model adjusted for age, total bilirubin, GGT, ALT, and region); Adjusted 3 (Cox-regression model adjusted for age, total bilirubin, GGT, ALT, sex, and year of birth); and Adjusted 4 (Cox-regression model adjusted for age, total bilirubin, GGT, and sBA).
ALT, alanine transaminase; 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; MRX, maralixibat; SAP, statistical analysis plan; sBA, serum bile acid.

CONCLUSIONS

- MRX treatment was associated with a 70% improvement (hazard ratio 0.305 [95% confidence interval: 0.189–0.491; p<0.0001]) in EFS in children with ALGS, when compared with the GALA natural history control cohort.
- This finding of improved EFS was robust, consistent across sensitivity analyses, and was not dependent on varying approaches to align the index time, prune for events following the index time, or propensity matching of each cohort.
- The regional subgroups and the overlapping sites subgroup (i.e. sites that offered both MRX clinical trials and participated in GALA) also showed a similar improvement in EFS for MRX-treated participants.
- These findings demonstrate the power of a natural history cohort to facilitate comparisons of long-term clinical outcomes in trials of rare diseases.

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DISCLOSURES/AFFILIATIONS

Please scan here to see all authors' disclosures and affiliations

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