EARLY RELEASED ABSTRACTS

Contents

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THU365* Global timing of hepatitis C virus elimination in high-income countries: an updated analysis

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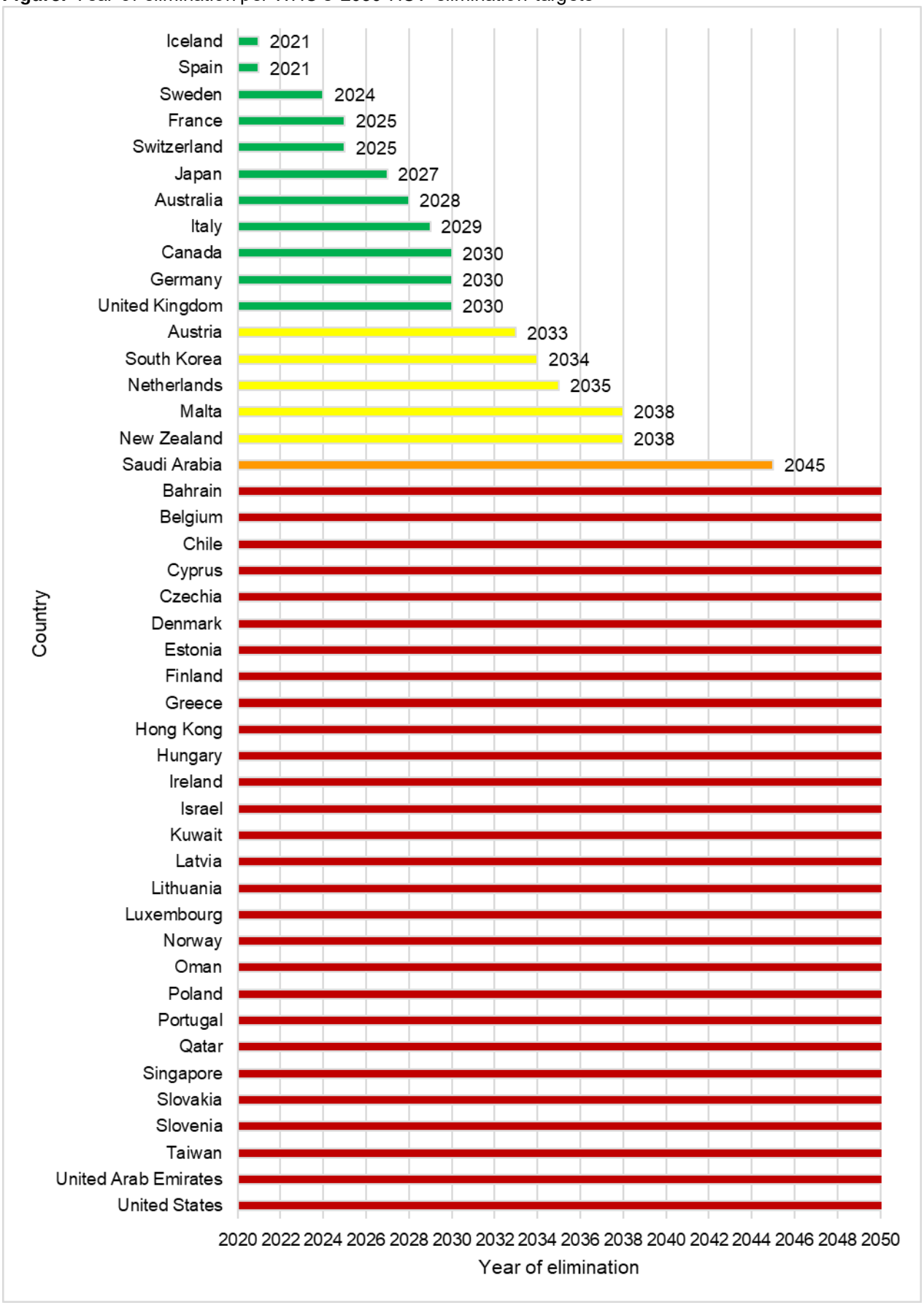
Background and aims: Elimination of hepatitis C virus (HCV) by 2030 as set out by the World Health Organization (WHO) may be attainable with the availability of highly efficacious HCV therapies. This study updates a previously published analysis on the timing of HCV elimination in 45 high-income countries based on WHO's targets for incidence, mortality, diagnosis, and treatment.

Method: Previously published Markov disease progression models of HCV infection for 45 high-income countries were calibrated to the latest available data on chronic HCV prevalence, and updated with number of annual new diagnoses (with reported data over 2017–2018) and treatments (with reported and projected data over 2017–2019). The latest reported or projected levels of diagnosis and treatment were defined as baseline and optimistically assumed constant in the future. Modeled outcomes until 2050 were analyzed to determine the year in which each country would meet WHO's HCV elimination targets for reduction in incidence (80%) and mortality (65%), and diagnosis (90%) and treatment (80%) coverage relative to 2015 levels. Earliest year in which all targets were met was defined as the year of elimination.

Results: Of 45 high-income countries studied, 11 (Australia, Canada, France, Germany, Iceland, Italy, Japan, Spain, Sweden, Switzerland, and the United Kingdom) are on track to meet WHO's HCV elimination targets by 2030; five (Austria, Malta, Netherlands, New Zealand, and South Korea) by 2040; and one (Saudi Arabia) by 2050. The remaining 28 countries are not expected to achieve HCV elimination before 2050. Of countries previously considered on track to eliminate HCV by 2030, one (South Korea) is now off track; of countries previously off track towards HCV elimination by 2030, three (Canada, Germany, and Sweden) are now on track. Most (29) countries saw no change since the previous analysis, with nine expecting an earlier time to HCV elimination, and seven expecting a later one. The incidence target, followed by mortality, remains the target fewer countries are expected to meet.

Conclusion: Assuming high-income countries will maintain their current levels of diagnosis and treatment, only 24% are on track to eliminate HCV by 2030 and 62% are off track by at least 20 years. If current levels of diagnosis and treatment continue falling, achieving WHO's 2030 targets will be even more challenging. With ten years remaining to meet these targets, expansion of screening and treatment is crucial to make HCV elimination possible.

Figure: Year of elimination per WHO's 2030 HCV elimination targets



WHO: World Health Organization; HCV: hepatitis C virus

THU366 Anticipated timing of elimination of hepatitis C virus in Canada's four most populous provinces

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Background and aims: While direct-acting antiviral therapy for hepatitis C virus (HCV) infection has made HCV elimination an attainable goal, current diagnosis and treatment levels in many high-income countries are insufficient to reach World Health Organization's (WHO) 2030 elimination targets. This study examines timing of HCV elimination in Canada's four most populous provinces which account for 86% of total population.

Method: A previously published model of HCV progression was populated with reported data for Alberta (AB), British Columbia (BC), Ontario (ON), and Quebec (QC). For BC, chronic prevalence and diagnosis data from 2018, and average annual treatments over 2015–2018 were used. For AB, ON, and QC, prevalence and diagnosis data from 2007 and 2011, respectively, and peak number of treatments in Canada, prorated for each province, were used. As base case, diagnosis (from 2017) and treatment levels were assumed constant, optimistically, to determine year of achieving WHO's 2030 HCV elimination targets for reduction in incidence (80%) and mortality (65%), and diagnosis (90%) and treatment (80%) coverage. Impact of 5% and 10% annual reductions in diagnoses and treatments were explored as less optimistic scenarios. The minimum annual reduction in diagnoses and treatments for delaying HCV elimination beyond 2050 was also calculated.

Results: Under base case, BC would reach WHO's HCV elimination targets by 2028, ON by 2030, AB by 2031 and QC by 2035. At 5% annual reduction in diagnoses and treatments, BC would be on track to eliminate by 2030, AB and ON by 2040, and QC by 2050; at a 10% reduction, only BC and ON would eliminate by 2050. At 14% annual reduction in diagnoses and treatments, no province would eliminate HCV by 2050.

Conclusion: Assuming that current levels of diagnosis and treatment are maintained, only BC and ON are on track towards WHO's 2030 HCV elimination targets among Canada's four most populous provinces. With many of the currently diagnosed already being treated, increasing and maintaining diagnosis levels is critical for achieving the treatment levels that would make timely HCV elimination a reality in Canada.

Figure: Progress towards HCV elimination targets

Province	Anticipated year of HCV elimination			Annual treatments needed over 2020–2030 for HCV elimination by 2030
	Base case (0% reduction*)	5% reduction*	10% reduction*	
Alberta	2031	2035	-	1,300
British Columbia	2028	2030	2033	3,900
Ontario	2030	2033	2044	5,300
Quebec	2035	2043	-	2,100

* Reduction in HCV screening and treatment
- No HCV elimination before 2050

THU375 Timing of hepatitis C elimination in the United States: estimating the year each state will meet the World Health Organization's elimination targets

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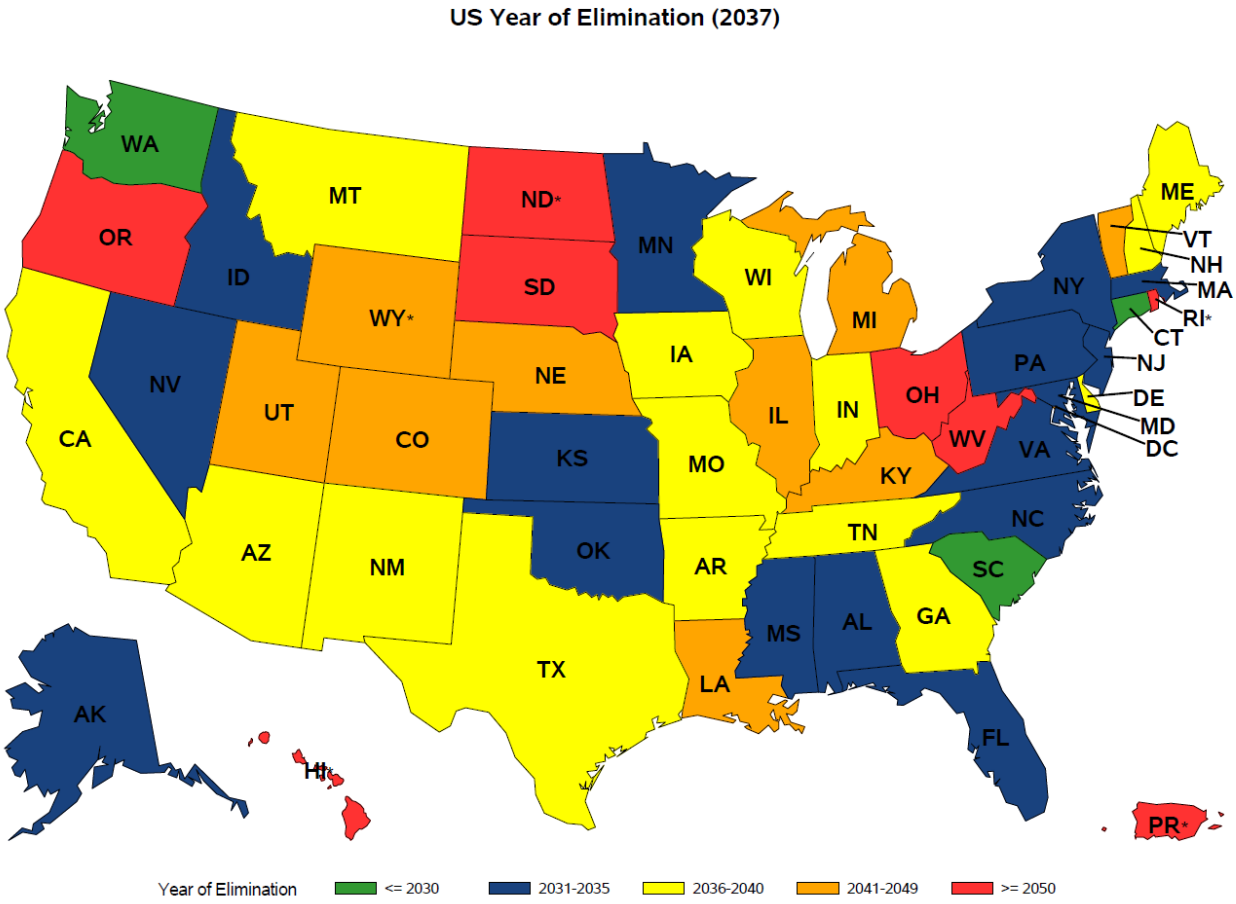
Background and aims: Short-duration, pan-genotypic curative therapies can accelerate the path to HCV elimination. This study assesses the progress and timeline of US states to achieve the 2030 HCV elimination targets set by the World Health Organization (WHO) for incidence, mortality, diagnosis, and treatment.

Method: A previously published disease-progression model was utilized to project the path to HCV elimination based on national and state-specific population, mortality, and HCV prevalence statistics. Data from two US large laboratory companies were used to estimate HCV prevalence from 2013 to 2017, including the diagnosed HCV population, newly diagnosed HCV cases and number of patients receiving antiviral treatments in 2017. Fibrosis-stage restrictions for treatment reported in 2017 for each state were also considered. The model then estimated the annual HCV-infected population by stage of liver disease, and HCV-related deaths. To inform the path towards HCV elimination, the model estimated the year each state would meet the WHO targets for: diagnosing 90% of the HCV-infected population; treating 80% of the eligible population; and reducing new HCV infections by 80% and HCV-related deaths by 65% relative to 2015 benchmark levels. We also calculated the minimum number of annual treatments necessary to achieve the treatment target for HCV elimination, over the course of 2020 to 2030.

Results: Overall in the US, the estimated year of achieving WHO elimination targets is 2037, with 2037 being the year the target for incidence reduction will be met, 2020 for reducing liver-related mortality, 2027 for diagnosis coverage and 2033 for treatment coverage. Only three of 50 states (Connecticut, South Carolina and Washington State, 6%) are on track to eliminate HCV by 2030. An additional 16 states (32%) were projected to eliminate HCV by 2035, 15 (30%) by 2040, 10 (20%) by 2050, and 8 (16%; Hawaii, North Dakota, Ohio, Oregon, Puerto Rico, Rhode Island, South Dakota, and West Virginia) not before 2050.

Conclusion: Our study suggests that the US is not on track to meet the WHO goals for HCV elimination by 2030 since only 6% of states are on track and 36% are off track by 10 years or more. As the year when all US states are expected to achieve HCV elimination targets is beyond 2050, strategies must be implemented to reduce HCV incidence, which include increased rates of screening, linkage to care, and unfettered access to curative therapy.

Figure:



*The estimation might be less accurate due to small number of HCV patients in the area

THU406 Integrated efficacy and safety analysis of GT1-6 treatment-naive, non-cirrhotic and compensated cirrhotic patients who received 8 weeks of glecaprevir/pibrentasvir

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Background and aims: The once-daily, all-oral, fixed-dose direct-acting antiviral combination glecaprevir (developed by AbbVie and Enanta) and pibrentasvir (G/P) is approved for chronic hepatitis C virus (HCV) infection in adults with genotypes (GT) 1–6. In the US, G/P is approved for an 8-week duration in HCV GT1–6, treatment naïve (TN), non-cirrhotic (NC) and cirrhotic patients (CC). In Europe, 8 weeks is indicated for HCV GT1–6 TN NC, and TN CC with GT1, 2, 4–6. In GT3 TN CC, 12 weeks is still recommended. This integrated analysis of label-consistent data evaluates the efficacy and safety of G/P for 8 weeks in NC and CC, TN patients.

Method: Data were pooled from TN patients with HCV GT1–6, receiving current label-consistent 8-week G/P across 8 Phase 2 and 3 clinical trials. Analyses were in intention-to-treat (ITT) and modified ITT (mITT; excluding non-virologic failures) populations.

Results: The table shows baseline demographics. Rates of sustained virologic response at Post-treatment Week 12 (SVR12) for NC patients with HCV GT1–6 were 97.6% (883/905) in the ITT and 99.2% (883/890) in the mITT populations. In NC and CC patients with HCV GT1–6, SVR12 rates were 97.6% (1218/1248) in the ITT and 99.3% (1218/1226) in the mITT populations. The SVR12 rates for NC and CC patients with HCV GT 1–6, excluding CC GT3 patients, were 97.6% (1157/1185) and 99.4% (1157/1164) in the ITT and mITT populations, respectively. Across all 3 groups, SVR12 rates remained high regardless of GT (94.3–100%); the GT3 ITT SVR rate was 95.4% for each group. The percentage of patients experiencing adverse events (AEs) was similar for all 3 groups (58–62%). The 3 most frequent AEs in each group were headache, fatigue, and nausea. In all groups, serious AEs were reported in <3% of patients and AEs led to study drug discontinuation in <1% of patients.

Conclusion: These data support 8-week treatment with G/P in TN GT1–6 patients, regardless of cirrhosis status, thus simplifying pre-treatment assessments for the selection of one short duration for most patients.

Table. Baseline demographics

	G/P for 8 weeks		
n (%) or mean ±SD	**GT1–6, TN, NC (n=905)**	**US Label GT1–6, TN, NC/CC (n=1248)**	**EU Label GT1–6, TN, NC/CC (excl. CC GT3) (n=1185)**
Male	492 (54)	709 (57)	660 (56)
White	708 (78)	993 (80)	931 (79)
Age, years	50.3±12.55	52.3± 12.47	52.4±12.62
GT 1 2 3 4/5/6	 352 (39) 202 (22) 217 (24) 53 (6)/19 (2)/62 (7)	 583 (47) 228 (18) 280 (22) 66 (5)/20 (2)/71 (6)	 583 (49) 228 (19) 217 (18) 66 (6)/20 (2)/71 (6)
Cirrhosis	NA	343 (27)	280 (24)

THU440 Real-world clinical practice outcomes in hepatitis C-infected patients with psychiatric and substance use disorders treated with glecaprevir/pibrentasvir for 8 or 12 weeks: a pooled analysis across nine countries

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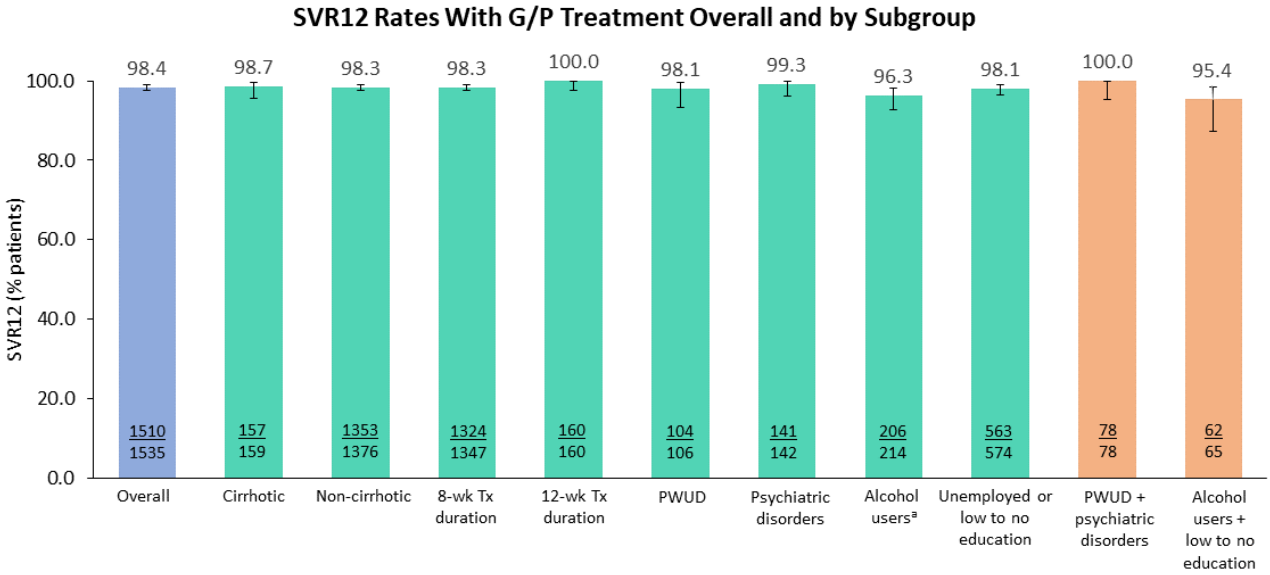
Background and aims: Barriers to treatment with DAAs still exist in patients with dual pathologies (ie, psychiatric and substance abuse disorders). Real world data are critical to inform clinical decisions and achieve WHO elimination targets. Glecaprevir/pibrentasvir (G/P) is approved for treatment of chronic hepatitis C virus (HCV) genotypes 1–6. In treatment-naïve patients, G/P was recently approved for shorter treatment duration (8 weeks) in patients with or without cirrhosis. We evaluated real-world effectiveness, safety, and patient-reported outcomes (PROs) of G/P in marginalized HCV-infected patients in ongoing post-marketing observational studies.

Method: Data were pooled from Austria, Belgium, France, Greece, Israel, Italy, Poland, Portugal, and Switzerland (13 Nov 2017–02 Oct 2019). Treatment naïve or experienced patients aged ≥18 years with or without cirrhosis were included. Patients received G/P consistent with local label and/or at treating physician's discretion (1608 [84%] received G/P for 8 weeks). Percentage of patients in the core population with sufficient follow up (CPSFU) who achieved sustained virologic response at post-treatment Week 12 (SVR12) was assessed overall and for each subgroup. The mean (SD) change in PROs (36-Item Short Form Health Survey [SF-36] mental [MCS] and physical component summary [PCS] scores) from baseline to SVR12 visit was reported (minimally important difference ≥2.5). Safety was assessed in patients receiving ≥1 dose of G/P.

Results: Of 1922 patients receiving ≥1 dose of G/P, 640 (34%) had used illicit substances, 184 (10%) had psychiatric disorders, 300 (18%) had a history of alcohol use, and 768 (44%) were unemployed or had low to no education. In the CPSFU population, the SVR12 rate was 98.4% (1510/1535) overall, 98.3% (1332/1355) in treatment-naïve patients, 98.9% (175/177) in treatment-experienced patients, and high (>95%) across all subgroups (**Figure**). Overall, mean change from baseline in MCS and PCS was 3.4 (10.5) and 2.1 (7.9), respectively, at SVR12 visit. In the total population (N=1922), 1 G/P-related serious adverse event (pericarditis) was reported; 6 patients (0.3%) discontinued G/P due to drug-related adverse events. The most common adverse events were asthenia (2.2%), fatigue (2.0%), and headache (2.0%).

Conclusion: The 8- or 12-week G/P regimen was highly effective and well tolerated in marginalized patients with single or dual pathologies infected with chronic HCV in the real world.

Figure.



Error bars represent 95% confidence intervals (Wilson's Score method). SVR12 rate was 92.9% (26/28) in patients treated with G/P for 16 weeks.
[a]Patients who consumed >2 drinks/day.
G/P, glecaprevir/pibrentasvir; PWUD, people who use drugs, SVR12; sustained virologic response at post-treatment Week 12; Tx, treatment; wk, week.

THU483 Quantitative magnetic resonance imaging predicts individual future liver performance after liver reception for cancer

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Background and aims: The future liver performance (FLP) of an individual undergoing surgical liver resection to remove cancer is critical for their survival and recovery. We report the development and clinical testing of a novel magnetic resonance image (MRI) post-processing tool that combines quantitative multiparametric MRI with anatomical liver segmentation to estimate FLP. This is intended to inform the assessment of individualised operative risk and augment patient and surgeon decision making prior to liver resection.

Method: This software combines iron-corrected T1 (cT1) mapping, previously demonstrated to correlate with fibroinflammation and predict clinical outcomes in chronic liver disease, with a 3D U-net pipeline to automatically delineate the liver volume prior to defining Couinaud segments based on anatomical landmarks. Interactive removal of these segments, along with any interactively-defined virtual wedge resections, allows accurate estimation of the future liver remnant (FLR) volume, which when combined with quantitative cT1 mapping, provides a prediction of FLP, termed the "HepaT1ca score". The ability of this score to predict post-operative morbidity, length of stay and regenerative capacity was evaluated in a prospective clinical trial (ClinicalTrials.gov NCT03213314).

Results: Of the 143 patients recruited, 135 underwent liver resection. 84% of participants had liver metastases from colorectal cancer, with the remaining having primary liver cancer or other secondary cancers. 21% of participants had cT1 values above the upper limit of normal (795ms) indicating increased risk of background liver disease. The HepaT1ca score showed a significant linear correlation with the modified Hyder-Pawlik score, an indicator of post-operative morbidity (adjusted $R^2 = 0.26$, $P < 0.001$), and liver regenerative performance (adjusted $R^2 = 0.46$, $P < 0.001$). Furthermore, in patients with an FLR below 90%, a high mean cT1 (> 795ms) was associated with a longer duration of hospital stay (median (IQR) of 6.5 (5.3-12) vs. 5 (4-7.1); $P = 0.0053$). cT1 also correlated with histological measures of inflammation and ballooning.

Conclusion: We demonstrate the utility of a non-invasive quantitative MRI approach for predicting post-operative liver performance. This has the potential to transform surgical decision-making and augment individualised risk assessment for patients undergoing liver resection for cancer.

Figure:

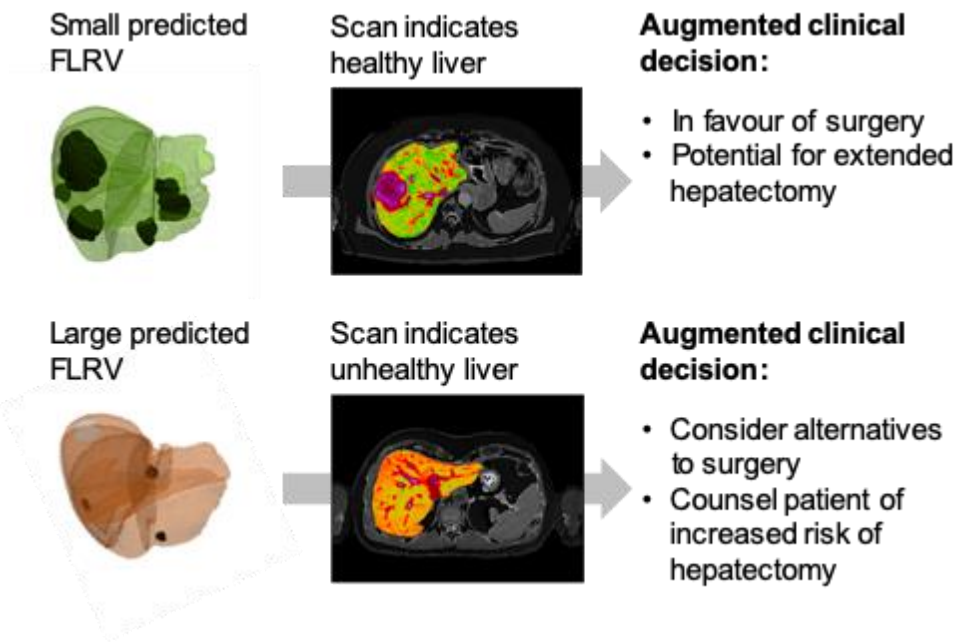

Figure: Concept diagram showing use of quantitative MRI in a clinical workflow highlighting exemplar case from the HepaT1ca study.

AS047 Increased survival in patients with hepatic encephalopathy treated with rifaximin-alpha in combination with lactulose: an observational study from UK clinical practice

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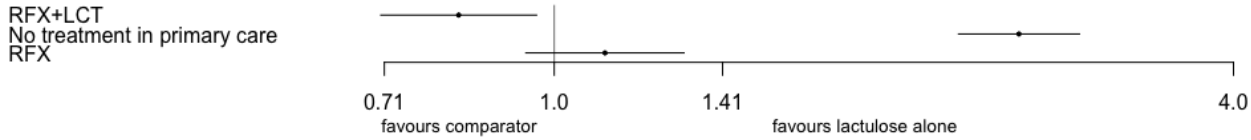
Background and aims: Hepatic encephalopathy (HE) is a neuropsychiatric complication of cirrhosis signalling hepatic decompensation. Overt HE episodes are medical emergencies that render patients' incapable of self-care, and frequently result in hospitalisation, coma, and/or death. In randomized studies, rifaximin-alpha (RFX) in combination with lactulose (LCT) significantly reduced the risk of HE episodes and overt HE-related hospitalisations compared with LCT alone. It has been postulated that treatment with RFX should increase life expectancy in these patients. In this study, our aim was to evaluate the impact of RFX treatment on survival in 'real-world' patients with HE in the United Kingdom (UK).

Method: Anonymised primary and secondary care health records from the Clinical Practice Research Datalink (CPRD) sourced HE patients treated with RFX and LCT, either as monotherapy or in combination, from 2003 to 2019 in primary care. Treatment was assumed to last for 28 days either side of prescription date. The primary endpoint was all-cause mortality (ACM) confirmed by national registration. Time to event from first proxy HE diagnosis (index) was analysed by extended Cox proportional hazards regression, where treatment and other covariates were modelled as monthly, updated, time-dependent parameters to maximise data availability.

Results: There were 4,669 patients newly diagnosed with HE, of which 61% were male, with a mean age of 59 years (SD 13), for whom 1,107 years of RFX, 1,500 years of LCT, and 1,157 years of RFX+LCT treatment were recorded. In total, 2,039 deaths were observed, at a rate of 271 per 1,000 person years. Compared to LCT-alone, RFX+LCT had an adjusted hazard ratio for ACM of 0.82 (95%CI: 0.70 to 0.96), while for RFX-treatment the aHR was 1.11 (95%CI: 0.94 to 1.30). Other ACM co-variables included age, gender, prior liver cancer, ascites, platelet count, estimated glomerular filtration rate, albumin and sodium.

Conclusion: Treatment with RFX+LCT improved survival compared to LCT-alone in routine clinical practice in the UK.

Figure: Forest plot for RFX+LCT, RFX, and no treatment in primary care versus lactulose



AS077 Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) to predict treatment response on NASH liver biopsy: a secondary analysis of the resmetirom randomized placebo- controlled phase 2 clinical trial

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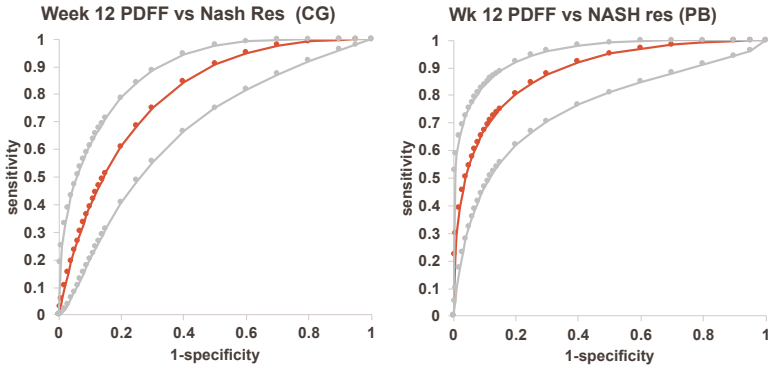
Background and aims: Resmetirom treatment resulted in significant reduction in hepatic fat as assessed by MRI-PDFF after 12 and 36 weeks that was associated with higher rates of NASH resolution compared to placebo on week 36 liver biopsy assessment. A few placebo patients who lost body weight also demonstrated MRI-PDFF reduction and NASH resolution. The aim of this secondary analysis was to examine the potential of reduction in MRI-PDFF to predict histologic response in NASH.

Method: The analysis included the subset of patients (n=107; placebo, n=34; resmetirom, n=73) who had MRI-PDFF at baseline, week 12, week 36 and week 36 liver biopsy in the Phase 2 randomized controlled trial of resmetirom versus placebo (pbo) for treatment of NASH. We examined the overall relationship in resmetirom plus pbo patients between PDFF and NASH resolution as evaluated by two blinded, independent central biopsy reviewers (CG, PB). The study cohort was assessed for those who had a ≥ 30, ≥40 and ≥50 % decline in MRI-PDFF between week 0 and week 12 as predictors of NASH resolution.

Results: Baseline characteristics have been reported (Lancet https://doi.org/10.1016/S0140-6736(19)32517-6). Among pbo (n=5,4 (CG,PB)) (3/5 pbo patients with ≳10% weight loss) and resmetirom (n=18) patients with NASH resolution, the mean week 12 fat reduction on MRI-PDFF was 56%, the optimal PDFF cutoff was 41.5% with a sensitivity of 0.82 (95% confidence interval (CI) 0.61,0.93) and specificity of 0.83 (95% CI 0.74,0.90), p<0.001, observed by both central readers (Figure). Compared to MRI-PDFF non-responders with <30% fat reduction (n=56), MRI-PDFF responders (≥30% fat reduction) (n=51) had significantly higher odds of NASH resolution (40% versus 3.7%) with odds ratio 9.1,18.0 (CG, PB) (95% CI 3.9, 82.3), p <0.0001. The odds of NASH resolution were higher with greater reductions in liver fat content, ≥ 40% and ≥50% MRI-PDFF reduction showing an OR of 16.5, and 25.3, respectively, compared to PDFF non-responders, p<0.0001. In patients with ≥50% fat reduction at week 12 (pbo=2; resmetirom= 22) 46% (CG) and 64% (PB) had NASH resolution with a component response driven primarily by ballooning and inflammation reduction. Change in ALT was not strongly associated with a histologic response.

Conclusion: MRI-PDFF response robustly predicted NASH biopsy response for resmetirom and pbo. Doses of resmetirom, 80 mg and 100 mg, used in the ongoing Phase 3 study MAESTRO-NASH had average PDFF reduction of 50% and 64%, respectively, and may predict higher rates of NASH resolution than observed in the Phase 2 study (27%) in which half of the resmetirom treated patients received a lower dose (60 mg).

Figure:


Week 12 PDFF vs Nash Res (CG)
sensitivity
1-specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0.2
0.4
0.6
0.8
Wk 12 PDFF vs NASH res (PB)
sensitivity
1-specificity

AS085 Twelve-month interim analysis of efficacy and safety of givosiran, an investigational RNAi therapeutic for acute hepatic porphyria, in the envision open label extension

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Background and aims: Acute hepatic porphyria (AHP) is a family of rare genetic diseases due to enzyme defects in hepatic heme biosynthesis. Induction of 5-aminolevulinic acid synthase 1 (ALAS1), the rate-limiting step in heme biosynthesis, can lead to accumulation of toxic heme intermediates 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), causing neurovisceral attacks and chronic manifestations. Givosiran, an investigational RNAi therapeutic, targets liver ALAS1 to reduce ALA/PBG and ameliorate attacks and clinical manifestations.

Method: ENVISION (NCT03338816) is an ongoing Phase 3 global, multicenter, randomized, placebo-controlled trial, evaluating the efficacy and safety of subcutaneous monthly doses of 2.5 mg/kg givosiran in AHP patients in a 6-month double-blind (DB) period and an open label extension (OLE) period (up to 30 months). During the OLE, patients received either 2.5 mg/kg or 1.25 mg/kg monthly givosiran. Outcome measures included composite annualized attack rate (AAR) requiring hospitalization, urgent care, or IV-hemin at home, ALA/PBG levels, hemin use, daily worst symptoms, and quality of life (QoL). Analyses were descriptive.

FRI024 Investigation of a composite imaging biomarker for identification of non-alcoholic steatohepatitis (NASH) patients in a Japanese population

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Background and aims: NASH pathogenesis is complex and composite biomarkers can improve identification of patients who are at risk of poor clinical outcomes. Liver*MultiScan*® uses multiparametric MRI to measure proton density fat fraction (PDFF) and iron-corrected T1 (cT1). PDFF quantifies hepatic steatosis while cT1 correlates with key histopathological features of NASH – ballooning, inflammation and fibrosis, and predicts clinical outcomes in patients with chronic liver disease. Herein, we report the performance of cT1 and PDFF in composite with non-imaging biomarkers, for the stratification of patients with suspected NASH in a prospective Japanese study cohort.

Method: Patients suspected of NASH underwent a 15-minute, contrast-free multiparametric MRI (Liver*MultiScan*, Perspectum Diagnostics). Liver biopsy was assessed using the NAFLD activity score (NAS) with NASH diagnosed as NAS ≥ 4 (ballooning ≥ 1, inflammation ≥ 1); fibrosis stage was assessed according to the Kleiner-Brunt criteria (F0-F4). The ability of the biomarkers to identify patients with (i) NASH and (ii) high-risk NASH (NAS ≥ 4 and F ≥ 2) was evaluated using area under receiver operating curve (AUROC) analysis, with logistic regression used to combine biomarkers.

Results: 97 patients were screened and underwent liver biopsy. Mean age was 60.1 years [28-82], mean BMI (±SD) was 29.0 (±4.7) kg/m^2, 38% were female and 54% had NASH. 23% were F1, 25% F2, 33% F3, and 16% F4 fibrosis; 45% were high-risk NASH. cT1 correlated with histological grading of fibrosis (r_s = 0.34, $p < 0.001$), inflammation (r_s = 0.47, $p < 0.001$), and ballooning (r_s = 0.45, $p < 0.001$); PDFF correlated with histological grading of steatosis (r_s = 0.68, $p < 0.001$). For identifying NASH, respective AUROCs for cT1 and PDFF were 0.76 (95% CI 0.66-0.86) and 0.77 (95% CI 0.68-0.87). For identifying high-risk NASH, respective AUROCs for cT1 and PDFF were 0.72 (95% CI 0.61-0.82) and 0.66 (95% CI 0.56-0.77). The optimal combination of cT1, PDFF, age and AST yielded a higher AUROC of 0.85 (95% CI 0.77-0.93) and 0.79 (95% CI 0.70-0.88) for identifying NASH and high-risk NASH, respectively (Figure 1).

Conclusion: In Japanese patients, cT1 outperformed PDFF for identification of high-risk NASH. Performance of cT1 was enhanced in combination with PDFF, age and AST for identification of NASH patients as well as those with significant fibrosis.

Figure:

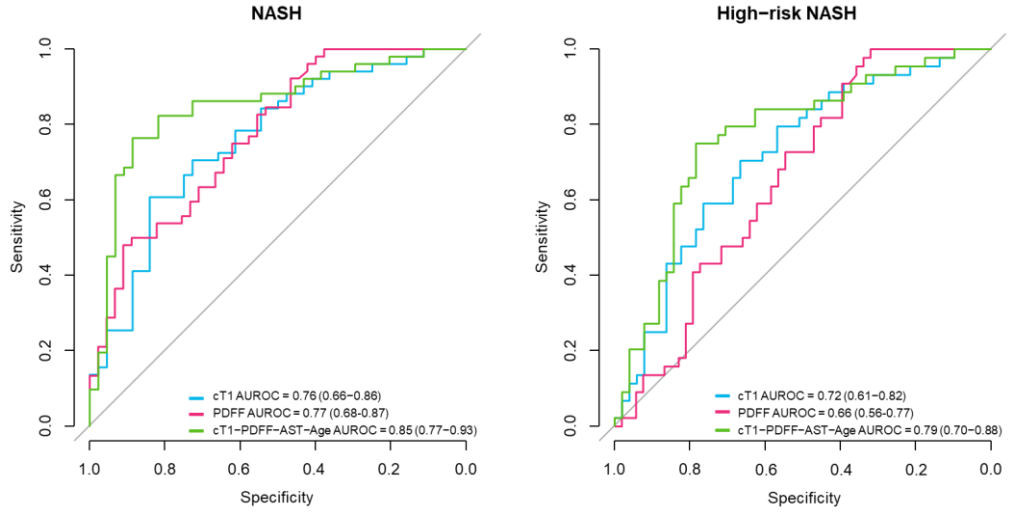

Figure 1. ROC curves to discriminate patients with NASH (left), and high-risk NASH (right)

FRI310 A phase 1/2 open label extension study of givosiran, an investigational RNAi therapeutic, in patients with acute intermittent porphyria

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Background and aims: Acute intermittent porphyria (AIP) is a rare genetic disease caused by an enzyme deficiency involved in heme biosynthesis. Induction of 5-aminolaevulinic acid synthase 1 (ALAS1) leads to accumulation of toxic heme intermediates, 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), resulting in potentially life-threatening, neurovisceral attacks and chronic symptoms. Givosiran, an investigational RNAi therapeutic, specifically targets ALAS1 to reduce ALA and PBG levels.

Method: A Phase 1 study evaluated the safety, tolerability, and pharmacokinetics/pharmacodynamics of givosiran (NCT02452372). Part C of the study was conducted in AIP patients experiencing recurrent attacks and included clinical activity as an exploratory endpoint. Patients completing Part C were eligible to enroll in the Phase 1/2 open-label extension (OLE) study (NCT0294983).

Results: As of April 19, 2019 (median time on study 24.7 months), givosiran administered at 2.5 mg/kg monthly robustly lowered ALA and PBG from baseline by >85% at 18 months in a sustained manner (median follow-up 19.8 months). Patients on givosiran had substantial mean reductions of >90% in annualized attack rate (AAR) and annualized hemin use, relative to Phase 1 Run-in. Serious adverse events (10) were reported in six patients, with one case of anaphylaxis assessed as definitely related to study drug. Adverse events occurring in more than three patients included abdominal pain, fatigue, injection site erythema, nausea, nasopharyngitis, headache, myalgia, diarrhea, injection site pruritus, and international normalized ratio increased. Seven patients had injection site reactions, all mild to moderate. No clinically significant laboratory changes were observed, including liver function tests.

Conclusion: In an ongoing Phase 1/2 OLE study, givosiran has shown an acceptable safety profile and has been associated with marked and sustained reductions in both AAR and annualized hemin use. Updated data from this study will be presented.

FRI351 Immunogenicity and efficacy of an HBV vaccine with an intrinsic checkpoint inhibitor

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Background and aims: $CD8^+$ T-cells are critical for control of HBV infection, but their activity is hampered by low antigen immunogenicity and T-cell exhaustion. HSV-1 glycoprotein D (gD), when genetically expressed as a fusion protein with target antigens, serves as a checkpoint inhibitor of the B and T cell attenuator (BTLA)-herpes virus entry mediator (HVEM) pathway, which acts early during T cell activation. HSV-1 gD thereby augments antigen-driven $CD8^+$ T-cell responses. We describe the immunogenicity and antiviral activity of two distinct chimpanzee adenoviral vector (AdC) vaccines containing key HBV sequences fused into gD.

Method: Adenoviral vectors of chimpanzee serotypes AdC7 and AdC6 expressing three different HBV sequences, which are conserved between HBV strains and carry human T-cell epitopes, were generated in HEK 293 cells. Each vector was injected at different doses intramuscularly into different strains of mice - in some experiments mice were primed with AdC6 and boosted 6-8 weeks later with AdC7. Blood- or spleen-derived lymphocytes were tested 2-8 weeks after immunization for $CD8^+$ and $CD4^+$ T-cell responses upon a brief in vitro stimulation with peptide pools representing the HBV sequences and then stained for T-cell surface markers and intracellular IFN-gamma and analyzed by flow cytometry. Individual epitopes in different mouse strains were determined using peptide matrices. An adeno-associated virus (AAV) vector of serotype 8 expressing the 1.3 HBV genome was injected i.v. at doses ranging from $1 \times 10^{10} - 3 \times 10^{11}$ genome copies (gc) into C57Bl/6 mice. Mice were vaccinated 4-8 weeks later or left untreated. HBV genome copies in serum were assessed before and after vaccination using a quantitative PCR.

Results: The vaccines were highly immunogenic and induced sustained T-cell responses. Multiple $CD8^+$ and $CD4^+$ epitopes were identified in different strains of mice including HLA-A2 transgenic mice. At low vaccine doses the response could be increased by a booster immunization with a heterologous AdC vector. Boosting furthermore increased the breadth of the T-cell responses. A single IM injection of the AdC6 vector produced sustained HBV DNA viral load declines of -2.0, -1.3 and -1.0 $\log_{10}$ mL through 8 weeks in animals injected with $1x10^{10}$, $1x10^{11}$ and $1.5x10^{11}$ gc of AAV8-1.3HBV, respectively.

Conclusion: These HBV vaccines induced high immunogenicity and significant antiviral efficacy; a Phase 1b trial in HBV-infected patients is in development.

SAT253 Multiparametric magnetic resonance imaging of liver and spleen is a reliable non-invasive predictor of clinically relevant hepatic venous pressure gradient thresholds and predicts failure of primary prophylaxis for variceal bleeding

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Background and aims: Multiparametric MRI (mpMRI) of the liver and spleen is a promising modality for non-invasive assessment of portal hypertension, offering a potential alternative to hepatic venous pressure gradient (HVPG) measurement, which is invasive and not widely available. Clinically relevant HVPG thresholds include (i) HVPG≥10mmHg, which defines clinically significant portal hypertension (CSPH) and predicts decompensation, (ii) HVPG>12mmHg, which predicts increased risk of variceal bleeding, and (iii) HVPG>16mmHg, which is associated with increased mortality. This study aims to evaluate the reliability of mpMRI of liver and spleen to predict clinically relevant HVPG thresholds (HVPG≥10mmHg, HVPG>12mmHg, HVPG>16mmHg) and development of variceal bleeding in a cohort of patients with chronic liver disease.

Method: Patients scheduled to undergo HVPG measurement for evaluation of portal hypertension were prospectively recruited for this IRB-approved study. All subjects underwent paired HVPG measurement and mpMRI (Liver*MultiScan*™, Perspectum Diagnostics, UK) to measure liver cT1 (assesses liver fibrosis and inflammation, corrected for iron) and spleen cT1 (assesses splenic congestion). Correlation between HVPG and mpMRI parameters (liver cT1 and spleen cT1) was evaluated using Pearson co-efficient and their performance for prediction of the various HVPG thresholds and variceal bleeding was evaluated using AUROC statistics.

Results: Forty subjects were enrolled, 50% males with median age of 64 years. Liver cirrhosis was present in 37 subjects (57% Child A). Median HVPG was 14 mmHg (IQR 12-17). 37 subjects had HVPG≥10mmHg (92.5%), 26 had HVPG>12mmHg (60%) and 12 had HVPG>16mmHg (30%). There was a weak but significant correlation between HVPG and liver cT1 (r=0.316, p=0.05) but not with spleen cT1. Liver cT1 was a good predictor for CSPH (AUROC 0.815, 95%CI 0.638-0.991) and a moderate predictor for HVPG>12mmHg (AUROC 0.737, 95%CI 0.564-0.911) and HVPG>16mmHg (AUROC 0.728, 95%CI0.567-0.889). Spleen cT1 was not a reliable predictor for any of the pre-determined HVPG thresholds. However, spleen cT1 was found to be an excellent predictor of variceal bleeding, particularly in the subgroup of patients on beta-blocker treatment (AUROC 0.950, 95%CI 0.854-1.000) with 100% sensitivity, 87% specificity, 67% PPV and 100% NPV at a cut-off value of 1395ms.

Conclusion: Multiparametric MRI is a potential non-invasive biomarker for assessment of portal hypertension. Liver cT1 is a reliable predictor for clinically relevant HVPG thresholds of HVPG ≥10, HVPG>12 and HVPG>16 mmHg. Spleen cT1 is an excellent predictor of patients at risk of failure of primary prophylaxis for variceal bleeding.

SAT256 Evolving imaging in biliary disease: quantitative magnetic resonance cholangiopancreatography findings correlate with the modified Amsterdam score in patients with primary sclerosing cholangitis

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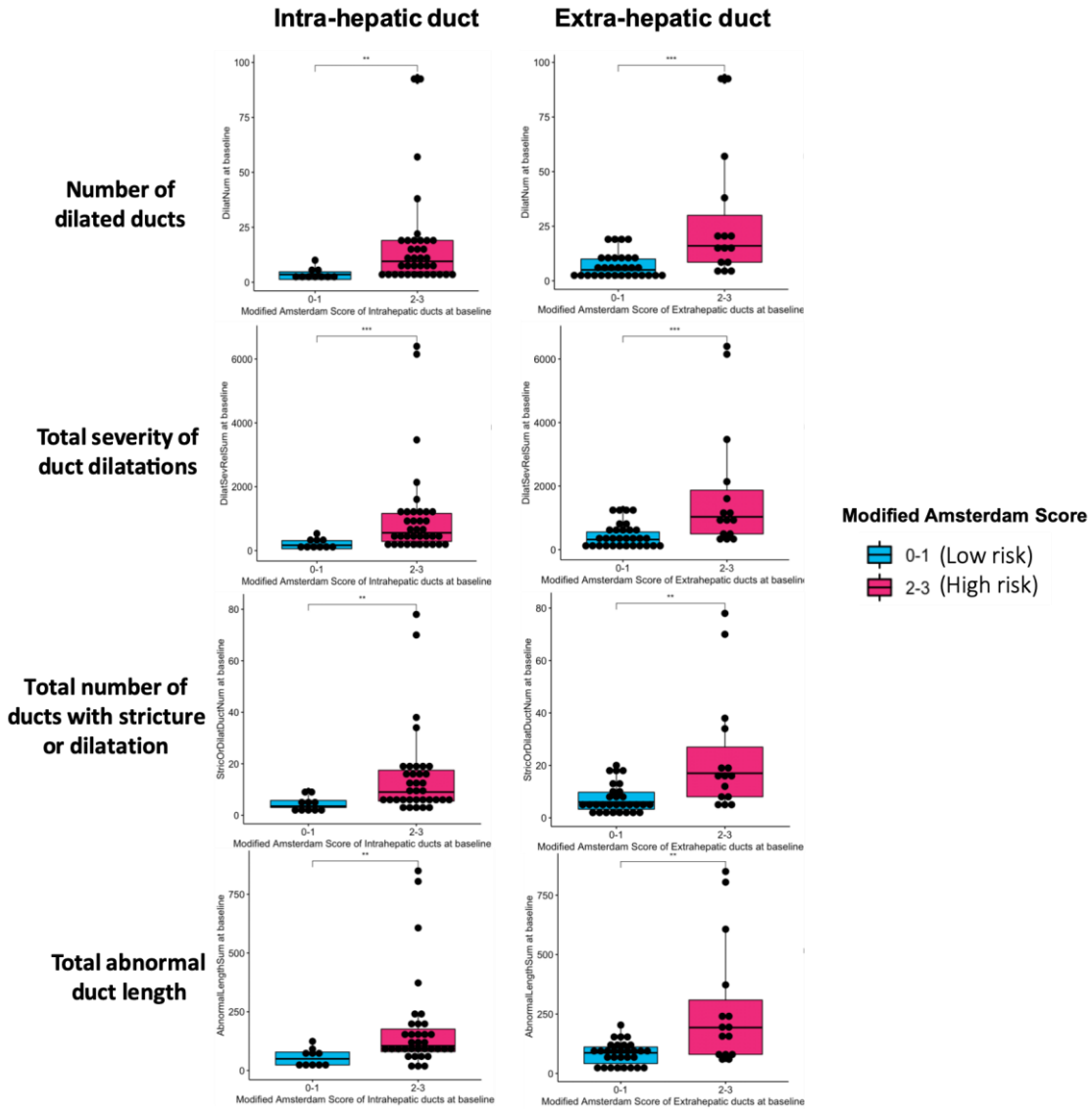
Background and aims: Quantitative magnetic resonance cholangiopancreatography (MRCP+) is a novel non-invasive imaging technique for quantifying biliary tree volume, duct diameters, and dilated/strictured regions in hepatobiliary disease. It is designed to address the limitations of traditional MRCP interpretation which can have large inter-observer variations. The aim of this study is to investigate the utility of quantitative MRCP in a prospective study of patients with primary sclerosing cholangitis (PSC) and evaluate its correlation with the modified Amsterdam cholangiography score.

Method: In this study, patients with established PSC (n=45) were recruited and scanned on a Siemens Verio 3T system with standardised MRCP imaging. The tubular structures of the biliary system were enhanced and quantified by MRCP+ using multi-scale Hessian analysis, gradient vector flow analysis, an intelligent path search algorithm and novel duct modelling algorithms. Each MRCP image was assessed by an experienced radiologist and evaluated using the modified Amsterdam score (mAms, intra-hepatic and extra-hepatic) to assess progression risk and categorized as low risk (0/1) or high risk (2/3).

Results: Assessment of intra-hepatic disease level measured by mAms revealed 10 PSC patients as low-risk and 35 as high-risk. High risk intra-hepatic patients were found to have a significant increase in the number of dilated ducts, the total severity of duct dilatations, total number of ducts with strictures/dilatations, and total length in abnormal ducts compared to low-risk PSC patients (16.7 vs. 3.7, $p<0.01$; 1083% vs. 205%, $p<0.01$, 15.1 vs. 4.5, $p<0.01$; 175 vs. 55mm, $p<0.01$, respectively). For extra-hepatic disease, 30 PSC patients were identified as low-risk, while 15 were assigned to the high-risk group. High-risk extra-hepatic PSC patients had a significantly higher number of dilated ducts (28vs. 7, $p<0.001$), the total severity of duct dilatations (1791% vs. 437%, $p<0.001$), total duct number with stricture/dilatation (23 vs.7, $p<0.01$), and total abnormal duct length (278 vs. 82mm, $p<0.01$) when compared to low-risk PSC patients.

Conclusion: Quantitative MRCP reveals significant correlations with both intra-hepatic and extra-hepatic abnormalities as assessed by the modified Amsterdam score in PSC patients by an expert radiologist. Our findings support the ability of quantitative MRCP metrics to contribute to an objective stratification of biliary disease.

Figure:


Intra-hepatic duct
Extra-hepatic duct
Number of dilated ducts
Total severity of duct dilatations
Total number of ducts with stricture or dilatation
Total abnormal duct length
DilatNum at baseline
DilatSevRelSum at baseline
StricOrDilatDuctNum at baseline
AbnormalLengthSum at baseline
Modified Amsterdam Score of Intrahepatic ducts at baseline
Modified Amsterdam Score of Extrahepatic ducts at baseline
0-1
2-3
Modified Amsterdam Score
0-1 (Low risk)
2-3 (High risk)

SAT271 Quantitative magnetic resonance cholangiopancreatography imaging in patients with primary sclerosing cholangitis - feasibility and preliminary analysis for prediction of clinical outcomes

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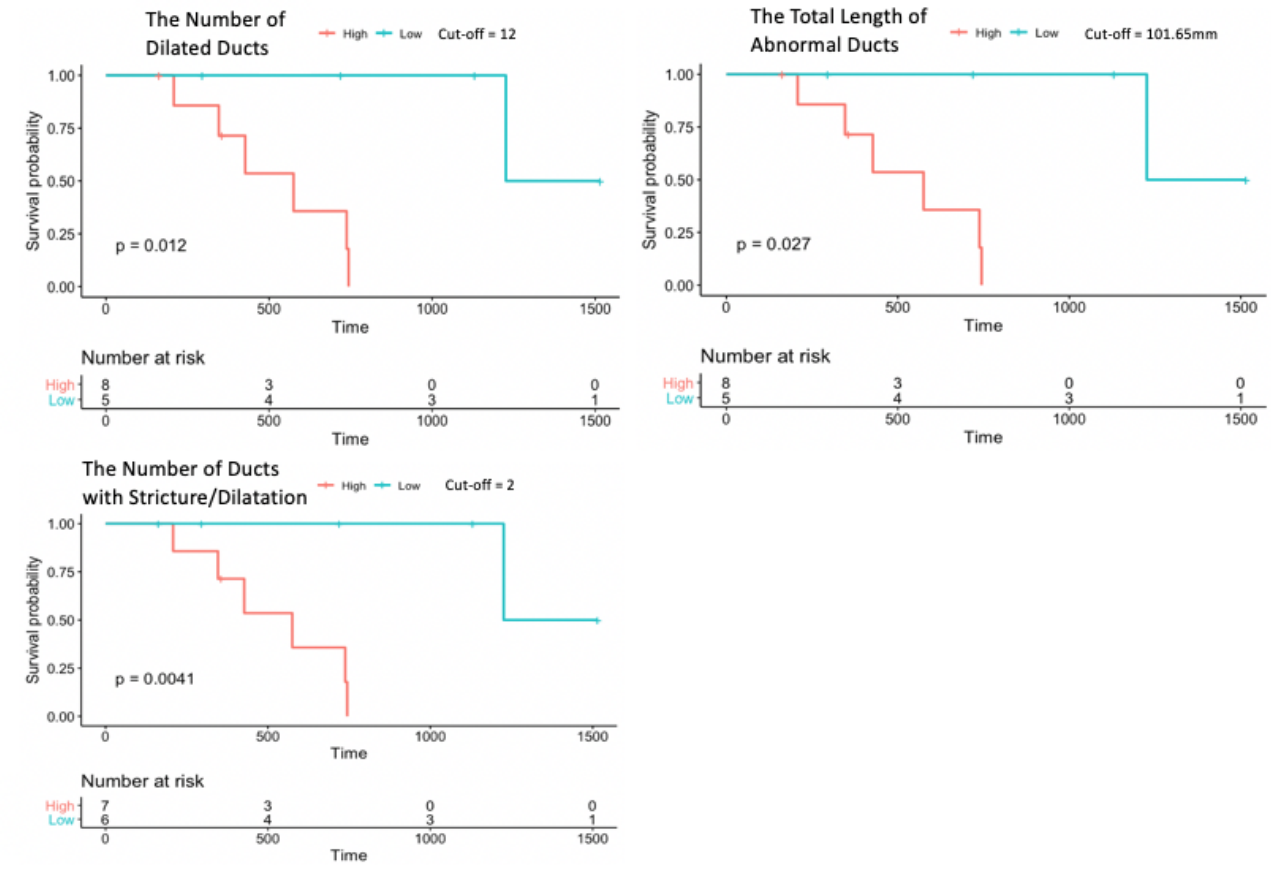
Background and aims: Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging technique commonly used for the evaluation of biliary disease. Despite its widespread use, MRCP relies on subjective assessments, lacking robust quantitative metrics and cannot predict the onset of liver related events. Quantitative MRCP (MRCP+™) is a novel technique that can quantitively assess biliary tree metrics. This study sought to understand the utility of MRCP+ in predicting clinical outcomes for primary sclerosing cholangitis (PSC).

Method: In this retrospective study, 35 PSC patients (69% Male; 82.9% Caucasian; mean age 54 years [7-70]) underwent standardised MRCP imaging. Images were post-processed using MRCP+ software, which enhances and quantifies the tubular biliary structures. The underlying algorithms combine an intelligent path search algorithm and novel duct modelling algorithms. The duration (in days) between the date of clinical event (liver transplant surgery or death) and the date of MRCP scan was calculated for the survival analysis; the Cox regression and Kaplan-Meier Estimator have been used to investigate the utility of MRCP+ derived metrics in predicting clinical outcomes.

Results: From the 35 patients, 13 (37%) PSC patients experienced a clinical event. The Cox survival analysis showed that MRCP+ derived metrics (the number of dilated ducts, the number of ducts with stricture or dilatation, and the total length of abnormal ducts) predicted the probability of a clinical outcome (either liver transplantation or death) (p=0.048, 0.046 and 0.037, respectively). Optimal thresholds (of 12, 2 and 102mm, respectively) of the above-mentioned MRCP+ metrics were calculated and applied. Low-risk patients (values below cut-off) had significantly higher liver-event-free survival than high-risk patients (values above cut-off) (p=0.012, 0.0041 and 0.0027, respectively) (Figure 1).

Conclusion: Quantitative MRCP (MRCP+) has been used for the first time to predict clinical outcomes in patients with PSC. Further analysis with a larger sample size and comparison to risk scores such as mayo risk score and UK-PSC risk score are in progress and will be presented at the meeting.

Figure: Kaplan-Meier Survival Curves for MRCP+ metrics.



Results: As of July 23, 2019, 93 patients entered the OLE: 56 (placebo/givosiran=29; givosiran/givosiran=27) received 2.5 mg/kg monthly givosiran, and 37 (placebo/givosiran=17; givosiran/givosiran=20) received 1.25 mg/kg. In givosiran patients (both doses), median AAR was 1.1 (range: 0–20.5) through Month 12. In placebo patients who crossed over to givosiran in the OLE, median AAR (DB=10.65; OLE=1.81) and proportion of attack-free patients (DB=17.4%; OLE=42.2%) were similar to the givosiran group in the DB period (median AAR=1.04; attack free patients=48.9%). In addition, sustained lowering of ALA/PBG in the OLE was accompanied by reductions in hemin use, daily worst pain and analgesic use, and improvements in QoL. Among patients on givosiran through Month 12, 62% had ≥1 drug-related adverse event (AE) and 3% had ≥1 drug-related serious AE. There were no new AEs leading to discontinuation and no deaths. No new safety concerns occurred in the OLE. There was a trend toward increased efficacy with the 2.5 mg/kg dose compared to 1.25 mg/kg dose, and safety was acceptable at both doses.

Conclusion: In an ongoing Phase 3 study, givosiran 2.5 mg/kg monthly demonstrated maintenance or enhancement of clinical efficacy and an acceptable safety profile consistent with that observed in the 6-month DB period.

SAT295 Early treatment of hepatitis C virus improves health outcomes and yields cost-savings: A modeling study in Argentina

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Background and aims: Patients with hepatitis C virus (HCV) face increased healthcare costs due to hepatic and extrahepatic complications. The new all-oral direct-acting antivirals have dramatically improved the sustained virological response (SVR) rates. Achieving SVR has shown to increase health benefits and reduce medical costs.

While treatment in early stages of liver fibrosis has been shown to reduce liver-related complications and lower healthcare costs compared to treatment in later disease stages, it is often delayed and patients in early fibrosis stages have limited access to effective treatment. Thus, this study evaluated the clinical and economic impact of treating patients in Argentina with HCV at early vs late stages of liver disease.

Method: A Markov model of the natural history of HCV was used to forecast liver-related and economic outcomes over a lifetime from the perspective of Argentina's social security sector. Health utilities and transition probabilities were drawn from published literature. Treatment attributes and patient demographics were based on registrational clinical trials of glecaprevir/pibrentasvir. Costs were based on tariffs from Argentina's social security system. Analyses were conducted for patients with HCV genotypes 1-6 and different fibrosis stages of liver disease: mild (F0–F1); moderate (F2–F3), and compensated cirrhosis (F4). Health outcomes included lifetime risks of compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT), and liver-related death (LrD). Other outcomes included lifetime costs and quality-adjusted life years (QALYs), both discounted at a 5% rate.

Results: In this simulated model, treating HCV infection at early stages of fibrosis appeared to reduce the risk of CC, DCC, HCC, LT and LrD (Table). Delaying treatment increased long-term total lifetime costs and provided fewer QALYs. Early treatment was a dominant strategy regardless of time of delay as it delivered more QALYs at lower costs.

Conclusion: This analysis suggests that treating HCV at early stages improves health outcomes and reduces the total cost in Argentina. Hence, clinical and policy decision-makers should avoid delays and restrictions in HCV treatment.

Figure:

Outcome	Liver fibrosis stages		
	Mild (F0-F1)	Moderate (F2-F3)	CC (F4)
CC Risk (%)	7.2	17.6	100.0
DCC Risk (%)	2.0	6.1	8.3
HCC Risk (%)	0.9	2.6	27.7
LT Risk (%)	0.2	0.6	1.9
LrD Risk (%)	1.8	5.8	30.7
SVR (%)	97.9	97.9	98.9
Total Costs (AR$)	954,018	967,673	1,437,816
Total QALYs	11.5	9.9	7.5