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ABSTRACT

1 | TENOFOVIR-DF THERAPY PREVENTS HEPATITIS B VERTICAL TRANSMISSION IN HIGHLY VIREMIC MOTHERS WITHOUT HBV IMMUNOGLOBULIN FOR INFANTS

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Background: Maternal tenofovir disoproxil fumarate (TDF) in combination with an infant's passive-active immunoprophylaxis is recommended by WHO for mothers with HBV-DNA >200,000 IU/mL. Because of the shortage of immunoglobulin (HBIg) in many developing countries, we aimed to study maternal TDF therapy initiated in the second trimester with an infant's HBV vaccination and omission of HBIg for preventing mother-to-child transmission (MTCT). **Methods:** In a multicenter RCT from 6/4/2018 to 2/8/2022, we randomly assigned CHB mothers with HBV-DNA >200,000 IU/mL (ratio, 1:1) to receive TDF from gestational weeks 14-16 (experimental group) or week 28 (control) to delivery. All infants received active immunoprophylaxis and HBIg was only given to infants in the control group. The primary outcomes were the congenital defects/malformation rates and MTCT rates (i.e., HBsAg+ or HBV-DNA >20 IU/mL) at the infant's age of 28 weeks. Secondary assessments were safety analyses (ClinicalTrials.gov: NCT03476083). **Results:** Of the 280 HBeAg+ mothers enrolled, 265 mothers and 269 infants completed the study (95% retention). The participants' characteristics are shown in Table 1. At delivery, a significantly lower median (IQR) HBV-DNA level (log_{10} IU/mL) was noted in the experimental group (2.37 [1.88, 3.08] vs 3.62 [2.86,4.59]; p< 0.001), with a similar trend in the percentage of mothers with HBV-DNA <200,000 IU/mL (99.2% vs 94.2%; p=0.04). The congenital defect rates did not differ significantly between groups (3.1% [4/131] vs 6.4% [9/141]; p=0.22). At the postpartum week 28, 128/128 and 137/141 mother/infant dyads in the experiment and the control groups were analyzed, respectively. The per-protocol analysis revealed 0% of MTCT in both groups. The maternal HBeAg/HBsAg (-) rates did not differ significantly between groups. TDF was well-tolerated without discontinuation from severe adverse events (SAEs). Safety parameters were comparable both in frequency and severity between the two groups including estimated glomerular filtration rates during treatment, postpartum ALT flares, and SAEs. **Conclusion:** In highly viremic CHB mothers, we observed that TDF initiated at gestational weeks 14-16 reduced MTCT to 0% when infants received HBV vaccines without HBIg, which also had similar safety outcomes when compared to those of mothers who initiated TDF at gestational week 28. Our data support

4708 | AN OPEN-LABEL, PHASE 1 STUDY TO EVALUATE THE PHARMACOKINETICS (PK) AND DRUG-DRUG INTERACTIONS OF SETANAXIB TABLETS IN HEALTHY ADULTS

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Background: Setanaxib is an investigational nicotinamide adenine dinucleotide phosphate oxidase 1/4 inhibitor (Calliditas Therapeutics Suisse SA) in development for treatment of primary biliary cholangitis (PBC). Setanaxib ≤800 mg daily was well-tolerated in a phase 2 trial in PBC.[1] This phase 1 study aimed to assess the PK and drug-drug interactions of setanaxib tablets, to support dose selection for the upcoming phase 2b/3 trial in PBC. **Methods:** This open-label study (NCT04327089), conducted Jun–Oct 2020 (Part 1) and Sept 2020–Apr 2021 (Part 2), assigned healthy adults to one of seven cohorts receiving setanaxib 400 mg tablets at doses ≤1600 mg/day (**Table**). Included participants were aged 18–49 years, smoked ≤5 cigarettes/day, weighed ≥45 kg, and had a body mass index 18.0–35.0 kg/m^2. Primary objectives were to assess: PK and dose proportionality of setanaxib and its main active metabolite, GKT138184, after single-dose administration (Part 1); safety after setanaxib twice daily (BID) for 10 days and potential drug-drug interactions when setanaxib is co-administered with a cocktail of substrates for either cytochrome P450 [CYP] enzymes or organic anion transporters [OAT]) (Part 2). **Results:** Part 1 recruited 30 participants (50.0% female); Part 2 recruited 34 participants (47.1% female). Two participants withdrew from cohort 7 prematurely. An approximate dose-proportional exposure increase was seen following single-dose setanaxib 400–1600 mg (fasted). Geometric means (GM) C_{max} / $AUC_{0-\infty}$ for cohort 4 were: 48.4 μg/ml / 208.0 h*μg/ml (setanaxib); 5.4 μg/ml / 41.8 h*μg/ml (GKT138184). For cohort 6, GM C_{max} / AUC_{0-24} at steady state were: 27.3 μg/ml / 193.0 h*μg/ml (setanaxib); 3.9 μg/ml / 38.1 h*μg/ml (GKT138184). GKT138184 exposure was ~20% that of setanaxib across all cohorts. In cohort 7, setanaxib 800 mg BID increased the exposures <2-fold for the probe substrates for CYP2C9, CYP2C19, and OAT3, and <1.3-fold for the probe substrates for CYP3A4 and OAT1. A total of 33 treatment-emergent adverse events (AEs) were reported by 24/64 participants; the most common was headache (13/33). No serious AEs were reported. **Conclusion:** Setanaxib ≤1600 mg was well-tolerated when administered as either single-dose or BID for 10 days, supporting the use of similar doses in a phase 2b/3 trial in PBC.[2] Single-dose PK were approximately dose-proportional over the dose range studied. At 800 mg BID, setanaxib may be considered a weak inhibitor of CYP2C9, CYP2C19, and OAT3, but not an inhibitor of CYP3A4 or OAT1. **1.** Huang J *Hepatology* 2019;70:777A–9A **2.** Jones D, submitted abstract ID 32296

Table. Study dose cohorts

	Cohort	n	Setanaxib dose	
			8am	8pm
Part 1 (fasted; single dose)	1	6	400 mg	NA
	2	8	800 mg	NA
	3	8	1200 mg	NA
	4	8	1600 mg	NA
Part 2 (fed; BID D1–10)	5	8	800 mg	400 mg
	6*	8	800 mg	800 mg
	7*	18	800 mg	800 mg

*Dosage and administration of setanaxib were identical in cohorts 6 and 7; participants in cohort 7 additionally received cocktails of single-dose midazolam, losartan + omeprazole (D-4 + D6) and adefovir + sitagliptin (D-2 + D8) to assess interactions with setanaxib. BID: twice daily; D: day; NA: not applicable.

Disclosures:
Cédric Szyndralewiez – Genkyotex SA: Former employment;
Bart Laurijssens – Calliditas Therapeutics AB: Consulting;
Stefan Carlsson – Calliditas Therapeutics AB: Employment; Calliditas Therapeutics AB: Stock Shareholder;
Richard Philipson – Calliditas Therapeutics AB: Employment; Calliditas Therapeutics AB: Stock Shareholder;

4709 | PRIMARY BILIARY CHOLANGITIS CASE-FINDING: AN ITALIAN MULTICENTER OBSERVATIONAL STUDY ON PATIENTS WITH INCIDENTAL FINDING OF ANTI-MITOCHONDRIAL ANTIBODIES

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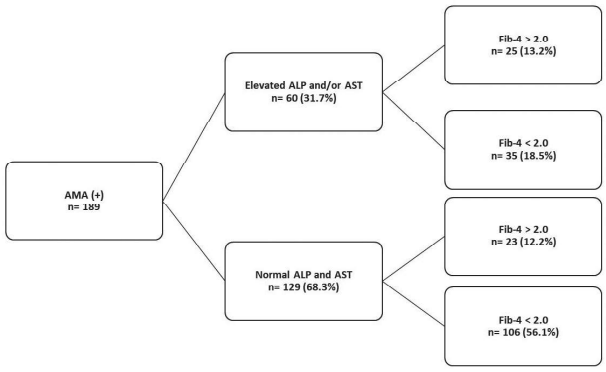
Background: Anti-mitochondrial antibodies (AMA) are a specific diagnostic marker of Primary Biliary Cholangitis



(PBC). The widespread use of auto-antibody test panels in non-hepatological settings allows incidental findings of AMA in patients without a history of liver disease. The aims of this multicenter observational prospective study were to assess the proportion of AMA positive subjects referred to hepatological evaluation and the evidence of significant liver disease found in these patients. **Methods:** From September 2020 to August 2021, 334 consecutive adult patients without a known history of liver disease were incidentally found positive for immunofluorescent AMA testing, with immunoblotting confirmed M2 positivity, during diagnostic evaluation mainly for rheumatologic or endocrinologic conditions at 18 Institutions in Italy. Referral of these subjects to hepatological evaluation was recorded until February 2022. Evidence of concomitant liver disease was assessed by serum liver enzymes and Fib-4 score (based on age, platelet count, AST, and ALT values). **Results:** One hundred forty-five subjects (43.4%) were not referred to hepatological evaluation and were lost to follow-up, while 189 patients (56.6%) were referred to hepatological evaluation and were analyzed. Female sex was predominant (n=162, 85.7%), median age: 63 years (range: 14-92). In 129 (68.2%) patients, alkaline phosphatase (ALP) and transaminase values were within the normal range. ALP resulted elevated in 47 (24.9%) patients: 248.6 ±157.8 IU/L, and normal in 142 (75.1%): 75.6 ±21.6 IU/L. AST levels were increased in 31 (16.4%) patients: 97.0 ±60.1 IU/L. In total, 60 patients (31.7%) had elevated ALP and/or AST values. Bilirubin levels were <2.0 mg/dL in all but 9 patients (4.8%). The Fib-4 score resulted <1.3 in 75 (39.7%), between 1.3 and 2.67 in 86 (45.5%), and >2.67 in 28 (14.8%) patients. Figure summarizes the proportion of AMA-positive patients with elevated or normal liver enzymes and a Fib-4 score > or <2.0. **Conclusion:** This real-world observational prospective study indicates that over 40% of subjects incidentally found positive for AMA are not referred to hepatological evaluation to assess the presence of PBC in clinical practice. Among AMA positive patients without a history of liver disease evaluated by hepatologists, about 1/4 to 1/3 show evidence of liver disease, suggestive of PBC. Patients without current evidence of PBC should be monitored and followed up. Our results indicate the need for an informational and educational campaign among rheumatologists and endocrinologists on the importance of a hepatological evaluation of patients with incidental AMA positivity.

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4710 | CHARACTERISTICS OF OVERLAP OF AUTOIMMUNE HEPATITIS AND PRIMARY BILIARY CHOLANGITIS IN JAPAN: A NATIONWIDE SURVEY

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Background: The International Autoimmune Hepatitis Group proposes that the overlap syndrome (OS)