

What is the evidence needed to extend label indication for approved MASH therapies in children

Regulatory perspective on MASH pediatric studies

Paris MASH Meeting 12 September 2025

Johannes Taminiau

European Medicines Agency

Pediatric Committee HCP member, Pediatric
Gastroenterologist

Disclaimer

“I attend this conference as an individual expert, and do not represent the PDCO EMA. The views expressed here are my personal views and may not be understood or quoted as being made on behalf of the PDCO EMA or reflecting the position of the PDCO EMA.”

Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH) 1 October 2024

Guideline only after availability of several registered drugs

- Diagnosis of MASH requires conduct of liver biopsy with histological evaluation, and the conduct of clinical studies should be mainly based on repeated biopsy results (portal-based chronic inflammation/fibrosis, and less ballooning)
- Young children (6-10 years) early in the disease process, candidates for lifestyle and dietary changes, of which success rates (with regard to weight loss) are usually higher than in adults
- Pharmacological treatment (off label) may limit disease progression
Regression of inflammatory changes is similarly considered to be higher (early onset and more aggressive phenotype of the disease compared to adults)

Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH) 1 October 2024

- Extrapolation in the development of medicines for pediatrics should be considered
- A distinction between adolescents and children may become relevant
Older adolescents could be included into adult studies if adequately justified
- Appropriate dose (under full consideration of the potential differences in pharmacokinetics in obese and NASH adolescents compared to adults) will be necessary
- Placebo-controlled studies may still be required, depending on the questions that remain to be answered, and may need to include liver biopsies

Adjustments and specifications despite no registered drugs

EMA agreed MASH PIP's

- Agreed Pediatric Investigation Plans (PIP) 21
- Modifications 6
- Compliance checks are only partial (NC) 3
- None finished
- Awaiting for adult results

PDCO current approach

Clinical

- Double-blind, placebo-controlled
- PK (either separately or as part of main study) in addition to safety and efficacy
- Primary endpoint: Proportion of subjects with fibrosis improvement (≥ 1 -stage improvement in NASH CRN) with no worsening of NASH (defined as ≥ 1 -point increase in hepatocellular ballooning or lobular inflammation), **rediscussion with PDCO before trial starts**
- Secondary endpoints: liver biomarkers, incidence of liver-related clinical outcomes, assessment of liver fat by MRI, MR Spectroscopy, ultrasound
- Study duration: usually 12 months but also 88 weeks, 96 weeks
- Deferred and to be conducted after studies in adults

Inclusion criteria

- Steatohepatitis: with a pattern of more severe steatosis 20% normal ALT
 - MRI-PDFF validated for children
 - CAP less validated
- Inflammation: predominant zone 1 periportal inflammation
 - ALT/GGT
- Fibrosis: Any stage including Stage F1 fibrosis as is important besides F2-F3
 - MRE
 - SWE
 - VCTE
- Liver biopsy still most informative (Age of screening)
 - Within 2 years
- At least one cardiometabolic risk factor

Primary Endpoints

Paucity of validated endpoints in children, but changes in ALT, GGT, and MRI-PDFF have been shown to be associated with changes in histological scores in randomized clinical trials

Steatosis without ALT elevation detection improvement tools for children

Fibrosis detection tools (MRE, SWE, VCTE)

Liver biopsy? Future NI endpoints and combinations possible and should be explored

Secondary and Exploratory Endpoints

Additional Measurements

- Ht-BW-BMI-Waist, Δ (Z-scores)-Tanner
- PDFF-MRE-SWE-VCTE-Platelets-Creat-Bil
- BP-TG-LDL-HDL-Gluc-HbA1c
- Safety issues

Stepwise PIP

Extrapolation

- Stepwise PIP: Early in drug development
- Extrapolation possible after adult Phase 3 efficacy data
- Differences between adults and children: Higher placebo effect, higher weight loss children in trials, PK/PD, TBW/LBW different ratio in obese children, LBW and BSA relate in a nonlinear manner to TBW recovery of CYP system in adolescents compared to adults.
- Adolescents 12-18 years could be allowed into Phase 3 adult trials especially post pubertal adolescents if confidence in drug after Phase 2 adult trial
 - Difficulties might be long duration, placebo, repeat liver biopsy, low numbers of adolescents

SOC

- GLP1 receptor agonists are approved for the treatment of obesity and diabetes in adolescents and have promising clinical trial outcomes in adults with MASH, priority for evaluation in children with MASLD
- GLP1 trials for obesity in adolescents EMA requests to test MASH parameters
- Pediatric MASH trials potentially add on design with GLP-1
- High placebo effect, high variable body weight loss

Longterm OLE

- Post Authorization
- 5 years studies?
- Longterm outcome multifocal variable related to MASH, DM, cardiac, cancer issues
- Early intervention: Effect of treatment of MASLD on diabetes risk: Investigate whether early intervention for MASLD or MASH in children with prediabetes reduces the incidence of diabetes
- More severe disease in children

