EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2017

Submission of comments on 'Concept paper on the need for the development of a reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)' (EMA/CHMP/197320/2017)

Comments from:

Name of organisation or individual
PSC Support **Martine Walmsley** **Chair of Trustees**

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	PSC Support is an active non-profit patient organisation based in the UK (www.pscsupport.org.uk), with members in over 60 countries worldwide, with an established PSC research funding programme. Our vision is to see a world without PSC. PSC Support has captured and published a report on more than 1,300 patient views on unmet needs and attitudes to research and potential treatments. We are in a unique position to provide patient input into this open consultation.	
	PSC Support welcomes the development of a Reflection Paper on the regulatory requirements for the development of medicinal products for PSC.	
	For the purposes of this response, PSC Support will limit comments to primary sclerosing cholangitis only, and not PBC/NASH.	
	PSC Support strongly suggests the scope of 'PSC' in the Reflection Paper includes **recurrent PSC (rPSC)**, which is a major concern for PSC patients after liver transplant. Scientific literature reports the frequency of rPSC to be around 20% although this figure varies, with even higher	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	rates reported. (Karlsen et al, 2017) Please add the following reference: Karlsen, Folseraas et al: Primary sclerosing cholangitis – a comprehensive review. Journal of Hepatology 2017. (In press)	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
51-52		Comment: PSC Support strongly supports the need to **establish and validate appropriate surrogate endpoints/biomarkers** in PSC research trials in place of histology. There is currently no validated surrogate biomarker for PSC. Relevant clinical endpoints such as death or liver transplantation occur too infrequently to be used as endpoints in phase 2 or 3 trials. It is therefore critical to identify appropriate surrogate endpoints that are reasonably likely to measure true clinical benefit. Proposed change (if any): Please consider/add the following reference: Ponsioen, CY. Endpoints in the design of clinical trials for primary sclerosing cholangitis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2017. (In press)	
53		Comment: PSC Support strongly supports the need to **establish suitable study populations** and this is particularly pertinent to PSC.	

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		A recent International PSC Study Group paper confirms significant phenotypic diversity across the global PSC patient population with implications for clinical trial design. Entry into clinical trials should be carefully stratified in order to limit the heterogeneity within studied cohorts. (Weismüller, Trivedi et al. 2017). Proposed change (if any): Please consider/add an additional reference: Weismüller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. *Gastroenterology*. 2017;152(8):1975-1984.	
54		Comment: PSC Support strongly supports the notion that the most efficient use of the PSC patient population is key in trial designs our rare disease. Proposed change (if any): none	
49-54		Comment: Discussion of the difficulties and opportunities for drug development in PSC should include consideration of co-existing Inflammatory Bowel Disease and Autoimmune Hepatitis features/status. (Dyson et al. 2015, Weismüller et al, 2017)	

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		Proposed **addition**: - Establishment of clear definitions and diagnostic criteria of PSC cohorts.	
57		PSC Support suggests the scope of 'PSC' in the Reflection Paper includes **paediatric PSC**. PSC has a chronic, progressive course in children, and nearly half of patients develop an adverse liver outcome after 10 years of disease. (Deneau et al, 2017). Proposed **change**: From: Specify needs and anticipated problems of Paediatric drug development (especially for NASH) Specify needs and anticipated problems of Paediatric drug development (for *both PSC and* NASH) Please consider the following reference: Deneau et al. The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration. Hepatology 2017, 66: 518–527. doi:10.1002/hep.29204	
77-81		Comment: We strongly support a **wide, global stakeholder group** made up of academia, pharmaceutical industry, scientific associations and other international drug regulatory	

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		authorities in the development of the Reflection Paper. Proposed change (if any): We would suggest that in Section 8: interested parties, the following stakeholders are also included: • The PSC Forum; • PSC patients/patient groups *(including but not limited to PSC Support, PSC Partners, PSC Patients Europe and ALBI France);* • Rare disease patient groups (such as EURORDIS); • ERN RARE-LIVER.	
82-122		Addition of the following references (as mentioned above). Deneau et al. The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration. Hepatology 2017, 66: 518–527. doi:10.1002/hep.29204 Dyson et al. Unmet clinical need in autoimmune liver diseases. Journal of Hepatology. 2015;62:208–218. doi: 10.1016/j.jhep.2014.09.010. Karlsen, Folseraas et al. Primary sclerosing cholangitis – a comprehensive review. Journal of Hepatology 2017. (In press). doi: 10.1016/j.jhep.2017.07.022 Ponsioen, CY. Endpoints in the design of clinical trials for primary sclerosing cholangitis. Biochimica et Biophysica Acta	

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		(BBA) - Molecular Basis of Disease 2017. (In press). doi: 10.1016/j.bbadis.2017.08.015 Weismüller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. *Gastroenterology*. 2017;152(8):1975-1984 doi: 10.1053/j.gastro.2017.02.038.	

Please add more rows if needed.