June 28th, 2011

Submission of comments on *"Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C"* (EMEA/CHMP/51240/2011)

Comments from:

Name of organisation or individual
Mrs. **Hilje Logtenberg-van der Grient MD**, Mr. **Ingo Van Thiel** and Mr. **Ivan Gardini** on behalf of **European Liver Patient Association (ELPA)** F. De Renesselaan, 57 B - 3800 Sint-Truiden, Belgium

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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	ELPA greatly welcomes the European Medicine's Agency intention to adopt a new guideline for the clinical evaluation of medicinal products for the treatment of chronic hepatitis C. In this context, ELPA refers to the new resolution by the WHO assembly WHA63.18 which defines viral hepatitis as a serious global public health problem where action needs to be taken with regard to health promotion, diagnosis and treatment. Guidelines on new drugs are an important tool to save many patients' lives, especially those most in need of treatment, who cannot wait for new drug approvals / licensing. **Who Are We Talking About?** People most in need are - regardless of origin, lifestyle, gender, sexual orientation, religion, or social background and financial status - those with advanced disease, and cannot wait for access to new drugs because they are at risk of progression, with limited or no current options. **The difficult-to-treat patients** **Trial Enrollment** Usually trials enrollment for licensing a new drug is done with Chronic Hepatitis C patients without co-morbidities, advanced cirrhosis, or contraindications against PEG-IFN and ribavirin. This "easy-to-treat" patient group could be considered the normal scenario. Unfortunately the real life	

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	scenario is quite different. The easy-to-treat patient group is becoming the smaller group in respect of the majority of the HCV patients. In real life medical trials, 30–70% of hepatitis C patients are excluded due to a vast variety of exclusion criteria, such as age, advanced cirrhosis, comorbidities, etc. *[Expert Consensus Conference. The screening for hepatitis C virus infection in adults in Italy. Istituto Superiore di Sanità. Rome, May 4-5, 2005.]* It is not an hazard to consider the new drug upcoming a sort of "elite drugs" just for some typologies of patients: the less complicated to treat. **Unmet needs** This means we have several patient groups and subgroups with unmet needs that are excluded from trials because they do not meet the enrollment criteria. **Special population** In our view we can consider - as special population the following groups • HIV/HCV coinfection • Hepatitis B/C coinfection • Advanced cirrhosis • Liver transplant setting • Pediatric population • patients with DAA failure • **Other subgroups excluded for medical or social problems** Within the above groups we could include other subgroups • Patients on methadone • Drug users • haemolytic anaemia	

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	• Haemophilia • renal dysfunction • comobidities • psychiatric problems • Contraindications against Peg-IFN/Ribavirin • Intolerance against Peg-IFN/Ribavirin • Cryoglobulinemia • Prisoners • Elderly patients • persistently normal ALT* * Many patient associations report that, paradoxically, patients with persistantly normal ALT are excluded from therapies because of "slow progression" of their disease and are advised to "wait for therapies with less side effects" **Patients in urgent need** There is no doubt that we need to focus our attention to those in urgent need, such as: • Patients with DAA failure • Decompensated cirrosis • Candidates for liver transplantation • Transplanted patients with rapidly progressive HCV recurrence • All above with or without HIV coinfection Why these priorities: for compassionate, humanitary, and social rights reasons; also, we would like to point out that in the next 3-5 years, the proportion of difficult-to-treat subgroups will grow in a dramatical way also because, in the meantime, the "easy-to-treat" patients groups will be cured	

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	more quickly. Naïve patients will become more rare and the minority group. In some countries, this is already a reality. **Liver transplant recipients and candidates** Study drugs in liver transplant candidates and recipients as soon as it is safe to do so. Hepatitis C is one of the leading indications for liver transplantation. Survival after transplantation is significantly reduced by recurrent HCV, which is difficult to treat; SOC is often ineffective or intolerable for transplant candidates and recipients. Liver-related mortality from recurrent HCV is significantly lower among transplant recipients who have achieved SVR than among those who were untreated or unsuccessfully treated (Rendina 2010). Transplant candidates and recipients are in desperate need of better HCV treatment; however, clinical trials of new HCV drugs in this population are generally last on the list, and postponed for years after drugs have already been approved. Clear regulatory guidance is needed to push sponsors into launching studies in transplant candidates and recipients, as well as in other high-risk populations. At a 2006 FDA meeting on development of novel agents for HCV treatment, panelists recommended that "approval of an effective agent in compensated subjects should not be adversely affected by poor outcomes observed in separate studies of decompensated liver disease" (Sherman 2007).	

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	HIV/HCV coinfection Hepatitis C–associated end-stage liver disease has become a leading cause of death among HIV-positive people in the United States and Western Europe, where HIV treatment is widely available (Weber 2006). HIV accelerates HCV progression, and SOC is less effective for coinfected people than for those with HCV monoinfection. Coinfected people need less toxic and more effective HCV treatments. Drug-drug interactions between DAAs and HIV drugs may limit the use of specific drugs in coinfected people; these must be fully characterized early in development to facilitate HCV treatment trials — and, ultimately, safe and effective use of DAAs in coinfected people. **Drug users and psychiatric disorders** Numerous studies have reported that drug users can be safely and effectively treated with SOC, especially when they are maintained on opiate substitution treatment such as methadone and buprenorphine (Bruggmann 2008; Dore 2010; Grebely 2010; Harris 2010; Hellard 2009; Sylvestre 2007, Lindenburg 2011, Manolakopoulos S 2010, Papadopoulos V 2010, Zanini B 2010). The same is true for people with psychiatric disorders: several studies have reported that people with psychiatric disorders can be safely treated once they are offered access to ongoing mental health care (including medication, if indicated) (Martin-Santos 2008; Schaefer 2003). Since depression, mood swings, hypomania, and mania are known side effects of interferon, it is wise for clinical trials to offer a baseline psychiatric assessment, regular screening for neuropsychiatric side effects, and mental health care during clinical trials to avert treatment discontinuation.	

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	Early Access Trials: multi-community overview: what we expect included in guidelines (ELPA, EATG, HCAB, and other community based groups) agree and strongly ask: In general: develop mechanisms to provide early access to DAA combination therapy for people who are ineligible for clinical trials and cannot wait for FDA approval. It is unacceptable that people with the most urgent need lack access to potentially life-saving therapies. **Although preapproval access to single or multiple DAAs poses medical, administrative, and regulatory challenges, it has been done with HIV and is certainly feasible for HCV**. Regulators, industry, physicians, and community members need to address and surmount barriers to early access. • Create clearer European rules for trials plus early access; • Early Access should start when phase 2b safety and efficacy data are available, ***during/ in parallel with*** phase III, prior to CHMP opinion; • Both make it obligatory and/or offer incentives for sponsors to conduct trials in difficult-to-treat populations within a certain timeframe, to obtain approval for easy-to-treat populations; • Create a FAST TRACK framework for providing access to people with advanced disease without endangering development programs in less advanced populations;	

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	• The safety database should not automatically be increased for "normal" patients if serious adverse events (SAEs) have only been observed in high-risk patients; SAEs in these high-risk patients should not automatically delay/halt trials of a new drug in "normal" patients, as SAEs are more likely in advanced disease/ comorbidities. **What Do We Need to Know?** • Safety, toxicity, side effects (especially in specific populations); • Some drugs may not work well for certain populations, so focus studies on appropriate drugs; • Studies in people with renal and hepatic impairment; • Drug-drug interactions with medications people take in real life (not limited to opiate substitution, ARVs) by the end of phase IIb and the beginning of Phase III trials; • Use in vitro/liver cell model testing for multiple DAAs, and to expedite clinical trials in advanced patients; • Closely monitor drug-drug interactions with immunosuppressants and DAAs in transplant patients; • Resistance to antivirals, and when/whether it disappears; • Trials should explore duration of therapy, and if it differs across populations (e.g., HCV monoinfected vs HIV/HCV coinfected); **Other** • Harmonization policies despite different national and local delivery systems;	

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	• Include community stakeholders at all levels. **Trials and Programs** • Finalized recommendations to establish early/expanded access & compassionate use programs on country-wide level; • Conduct clinical trials in well-defined, specific populations; • Difficult-to-treat patients should not be included in any trials which do not aim for an immediate clinical benefit (as in most phase 1 trials); • Prefer cohort-based vs. individual (name-based) early access programs; name-based programs should be protocolled; • Collect data on adverse events in cohort-based early access programs; • Control arm patients: prioritize access to single or multiple DAAs for trial participants in the control arms of clinical trials, and for those who did not achieve SVR. Cross-over or roll-over study designs should provide access to the experimental drug for people in the control arm. This approach should be broadened to include study participants unsuccessfully treated with single or multiple DAAs, providing that virtual monotherapy (a multidrug regimen containing only one active agent, causing rapid development of drug resistance) can be avoided. A cross-company registry of treatment experienced trial participants should be established, and these participants should be prioritized for enrollment into trials of DAAs from novel classes.	

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	• Post-approval observational trials that follow people for long-term SVR, resistance, disease status and quality-of-life for at least 3 years. • Important to include: pediatric patients, geriatric patients, diverse race/ethnicity, women, different stages of fibrosis/cirrhosis ; **Companies** Companies should be encouraged to • cross collaborate to facilitate best-in-class, multi-DAA trials; • conduct trials of novel HCV therapies in people most in need should already begin before approval is granted for their use, once results from Phase IIb studies are known, and once there are indications from earlier toxicology, pharmacokinetic, and drug-drug interaction studies that the specific agent, or agents under investigation will not have the potential for significant drug-drug interactions or other toxicities; • create a parallel track for trials in people with advanced disease; • prioritize the development of appropriate drugs for people with advanced disease, and people who are using additional medications for a range of other conditions; • involve the community in development plans and design of informed consent; • provide medications free of charge for early access programs.	

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	Other priorities also include: **Optimizing HCV care and treatment by giving nonspecialist providers the tools they need to successfully treat patients with HCV**. **Development of second- and third-line drugs effective against HCV with commonly occurring resistance mutations.** Adding a single DAA increases the likelihood of SVR for treatment-experienced people, but is not 100% effective. As an example, only 14% of null responders with cirrhosis achieved SVR after re-treatment with telaprevir plus SOC in Vertex's REALIZE phase III trial. An increasing population of people resistant to at least one drug, or class of drugs, could become a problem in the future. Cross resistance to HCV protease inhibitors has already been reported. Sponsors should prioritize drugs with a unique resistance profile and a high genetic barrier. **Development of drugs with activity against all HCV genotypes**. There are at least six HCV genotypes. Most new HCV drugs were designed to be effective against HCV genotype 1, because it is difficult to cure with peg-interferon and ribavirin, and it is predominant in the United States, Western Europe, and Japan (major pharmaceutical markets). As more people with genotype 1 are cured, and immigration patterns shift, the global distribution of HCV genotypes will change. It will not be possible to eradicate HCV without safe and effective drugs for all genotypes. **Full characterization of predictors and indicators of response and nonresponse to HCV treatment across populations.** Stopping rules may change as HCV treatment evolves. Reliable predictors of response will motivate people to continue HCV treatment, and facilitate reimbursement	

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	for response-guided therapy. In turn, accurate indicators of nonresponse will lower the risk of resistance, protect people against unnecessary treatment and its side effects, and save money. **Continue to characterize resistance to all classes of DAAs**. Further characterization of resistance mutations is needed to optimize HCV treatment with DAAs, although the clinical utility of resistance testing is not clear at present. Further assessment of clinical implications of HCV drug resistance is needed. One way to assess the impact of drug resistance would be to re-treat people who acquired drug resistance in monotherapy trials with the same drug, plus SOC. *[These comments are partially inspired by the "Community prospective document – EATG Sitges meeting 2001" and "HCV pipeline 2011" by Tracy Swan, Treatment Action Group]*	

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)*
Cover page, Keywords: SOC		**Comment:** What is considered now as standard of care (SOC)? Dual or triple therapies? If triple therapy, which drug will be used in the control arm?	
LINE 83-84		**Comment:** "as early as can safely" should be specified more **Proposed change (if any):** Introduce "by the end of phase II and the beginning of phase III trials"	
LINE 87		**Comment:** Good recommendation. There is another good recommendation from line 270 onward, but it comes a little too late and should first be mentioned here, too: **Proposed change (if any):** As the role in IL28B is still unclear in DAA-only treatment regimens, IL28B testing should be extended to such trials. Maybe add a short sentence here that it is ***"highly desirable to investigate whether IL28B also has a role in all-oral treatment regimens without pegIFN".***	
LINE 91		**Comment:** As in line 163, already mention here that it is important to investigate retreatment options for patients whose dominant population has NOT reverted to wild-type.	
LINE 99		**Comment:** WHO states 170 million HCV+, if we remember correctly. Is	

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		there any source or footnote for the 200 million?	
LINE 107		**Comment:** Literature is not always the same in such estimates, which source does this refer to?	
LINE 138		**Comment:** Difficult + open to interpretation. Actually, Telaprevir is the only first generation DAA which was tested in HCV null responders in the phase III trials. Boceprevir was only tested in partial responders and relapsers in the RESPOND-2 trial, but not in null-responders; it had weak results in null-responders in the phase II Respond-1 trial (2–14% to our knowledge). We should not generalize this statement, as null responders may end up being treated with a drug that was not properly tested for them.	
LINE 160-161		**Comment:** For instance, intravenous silibinin and host-targeted antivirals have a very high barrier to resistance, or might not even create any resistance at all. It is possible to mention these as examples?	
LINE 212-213		**Comment:** Very good! This is a remarkable opening to investigating trial drugs earlier in other groups. However, only "other genotypes" and HCV/HIV coinfection are mentioned as examples. **Proposed change (if any):** We suggest to also list "decompensated cirrhosis", "liver	

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		transplant recipients" and "patients awaiting liver transplant".	
LINE 268 - 278		**Comment:** Difficult. While this increases the safety of trials and makes sense as long as SVR is not the aim of the trial (proof-of-concept, as mentioned here). Please clarify if dose-ranging trials only include very early experimental trials (then we'd agree fully), or also more advanced phase II trials that aim for SVR (then we'd advise caution)? **Proposed change (if any):** As soon as trials are designed to achieve higher SVR, they should also include IL28B TT patients with advanced disease, who cannot wait for the approval of new drugs and for whom participation in a trial with the aim of higher SVR may be the last chance to survive without a liver transplant.	
LINE 295		**Comment:** Would you consider including patients with cirrhosis CHILD B and patients with contraindications?	
LINE 325-326		**Comment:** will there be literature/footnotes supporting this statement?	
LINE 335		**Comment:** Agree with general intent behind this strict rule. **Proposed change (if any):** However, we suggest to use a more neutral word such as "treatment failure" here. "Non-response" is very specific and somewhat misleading in this context, as it excludes	

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		relapse/breakthrough patients, who do achieve temporary negativity. Is this a rule which would also be applied to special population trials?	
LINE 382		**Comment:** Such data are expected to be available at the time of the marketing authorisation. **Proposed change (if any):** Such data is expected to be available ***before*** the marketing authorisation.	
LINE 404-408		**Comment:** *"suspicion based on theoretical consideration"* is somewhat vague and open to interpretation; better shorten this to "suspicion" which is more to-the-point. **Proposed change (if any):** Whenever there is a suspicion that a certain combination of compounds could be antagonistic, combination studies in vitro should be performed.	
LINE 455-466		**Comment:** We not familiar with the SWP guideline mentioned in lines 452-53, and this part is not clear: Should there only be combination toxicology studies "if there are specific concerns"? Shouldn't this be a general rule of caution for all combinations? Or is that already the case? Does the other guideline state that all new drug combinations first have to be tested in vitro and in vivo (animal) before being tested in humans? If it does, we suggest to still explicitly mention that here. The present document should be as self-explanatory as possible, instead of referring readers to a different guideline.	

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LINE 500		**Comment:** Telaprevir Studies seem confirm that IL28 is not a SVR predictor on such drug and IL28B data cannot be extended to all drugs. (Pol 2011)	
LINE 542		**Comment:** Latest data from EASL 2011 question the merit of lead-in treatment in several new DAAs (e.g. Telaprevir). Suggestion: Allow, but don't recommend lead-in. The way it is worded now, it sounds like a general recommendation. **Proposed change (if any):** "might" instead of "would"	
LINE 626		**Comment:** *"An alternative would be to investigate such combinations in patients with an immediate medical need that are deemed not to tolerate existing treatment options"* **Proposed change (if any):** We recommend this alternative become the priority option to facilitate access for patient with immediate medical need.	
LINE 651		**Comment:** Please clarify what is necessary to reach a proof-of-concept situation: In this context, "Proof-of-concept" appears stronger than "at least a characterization of SVR responses". We are confused because we thought "proof-of-concept" was already reached if there is any rapid response, even without an SVR, e.g. in the INFORM-1 trial? Or we are getting this wrong? In this special context, it is not exactly clear to us what is required to have a proof-of-concept situation. Multiple SVRs?	

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LINE 715		**Comment:** *"Such studies should be comparative and, at present, placebo controlled."* Recommend to offer therapy in the placebo arm after the observational period, if there is any advantage for the treated group.	
LINE 786		**Comment:** A head-to-head comparison between Peg-IFN lambda and Peg-IFN alfa-2a is ongoing (EASL 2011). According to interim results, Lambda seems to have fewer general side effects (e.g. flu-like symptoms), but higher liver toxicity (ALT+, bilirubin+) in higher doses. **Proposed change (if any):** If further results become available before this guideline is published, they might be included in this draft	
LINE 828		**Comment:** We have reservations about recommending a liver biopsy at baseline in all children as a general rule, before any treatment. Any possibility to recommend non invasive methods?	

Please add more rows if needed.