Meeting of Merck/MSD and EECA CAB,

June 13, 2012, Tbilisi, Georgia

MINUTES

Participants:

From Merck/MSD:
Paul Schaper
Murat Asik
Ekaterina Lukyanova

From EECA CAB:

Ehtiram Pashayev	Public Organization Against AIDS
Nofal Sharifov	Public Organization Against AIDS
Hovhannes Madoyan	Public Organization "Real World Real People"
Anahit Harutyunyan	Positive People Armenian Network
David Ananiashvili	Public organization "Georgian plus group"
Lasha Tvaliashvili	Public organization "Real People Real Vision"
Paata Sabelashvili	Georgian Harm Reduction Network
Zurab Danelia	Public organization «Union Tanadgoma»
Konstantine Rukhadze	Organization of people living with Hepatitis C
Marina Chokheli	Open Society Georgia Foundation
Evgeniya Kalinichenko-Katineva	Country Network of PLWH
Denis Marukha	League of PLWH in Moldova
Alexey Burlak	All-Russian Network of People Living with HIV
Svilen Konov	European Community Advisory Board (ECAB)
Gregory Vergus	International Treatment Preparedness Coalition in EECA region (ITPCru)
Denis Godlevskiy	International Treatment Preparedness Coalition in EECA region (ITPCru)
Sergey Golovin	International Treatment Preparedness Coalition in EECA region (ITPCru)
Andrey Zlobin	Russian Community Advisory Board (RuCAB)
Erika Matuizaite	Eurasian Harm Reduction Network (EHRN)
Aleksandr Hodanovich	Belorussian Community Advisory Board (BelCAB)
Dmitriy Sherembey	Ukrainian Community Advisory Board (UCAB)
Bohdan Zaika	Ukrainian Community Advisory Board (UCAB)
Tatyana Khan	East European and Central Asian Union of PLWH (ECUO)
Victoria Vinckler	Estonian Network of PLWH

Moderator: Denis Godlevskiy

Introducing the participants.

The first meeting with the company Merck/MSD.
Report regarding the history of EECA CAB. Dialogue is lacking at the regional level between the company and the community. Expression of thanks to the company for its participation in the meeting.

Presentation of research in the area of hepatitis C treatment

Merck/MSD and the result of the merger with Schering Plough. Business with clients in 140 countries. Several major trends in research: infectious diseases (HIV and HCV). Merck/MSD is one of the few companies that is actively working on research in the area of antibiotics and antifungal drugs.

The current standard treatment of HCV consists of pegylated interferon and ribavirin (PEG-INF+RBV). Boceprevir (BPV) is a new drug that will soon be available in the entire EECA region with the exception of Russia. The drug will appear in Russia last of all within the EECA region. This is due to new legislation which requires local research. All countries bordering on Russia will have boceprevir very soon, practically in this year. Its market name is Victrelis. The drug will be an addition to standard treatment with pegylated interferon and ribavirin. It prevents the formation of viral particles (it acts directly). Its effectiveness has been demonstrated both among naive and experienced patients. The drug was registered in the USA on 13 May 2011. Phase III Research conducted with naive patients is called SPRINT-2. Research conducted with experienced patients is called RESPONSE-2.

Triple therapy with a lead-in period (the first four weeks of therapy). Before boceprevir is prescribed, time is available that can allow take into consideration treatment tolerance, how to coordinate treatment, and how best to add the third agent. SPRINT-2 Research
3 groups: first 4 weeks PEG-INF alfa 2b+RBV for all groups, then
Group 1: PEG-INF+RBV + placebo for 44 weeks
Group 2 treatment depends on the response (response guided therapy): PEG-INF+RBV + BPV for 24 weeks, if the viral load was detected between weeks 8 and 24, then patients received a further 20 weeks PEG-INF+RBV + placebo
Group 3: PEG-INF+RBV + BPV for 44 weeks (triple therapy).

During the course of treatment, an individual approach for each patient was sought, and the long and short courses of treatments were compared.
Pegintron and Rebetol were used in standard therapy. Individual doses of ribavirin were used based on body weight.
The criteria for inclusion: patients should not be receiving antiviral treatment at the moment of inclusion. Patients with a co-infection of HIV/Hep B were not included in the research. Patients were delineated by race (it has been shown that blacks respond worse to any treatment). HCV genotypes: only 1a and 1b.
Effectiveness – 40% in the placebo group, 67% in the response guided therapy group and 68% in the triple therapy group.

For patients who responded well after 8 weeks, the effectiveness was markedly higher (the earlier the patient responds, the better the general result). If a patient responds well, it may be possible to

shorten the course of treatment. Those patients who responded poorly before, responded poorly to treatment in principle. Those who responded well in the beginning, responded well overall.
Factors in success: the viral load level at the beginning of treatment, young age, absence of cirrhosis (the results with cirrhosis are 2.5 times worse).

Question: Has there been a breakdown with interleukin?

***Answer*:** Yes. It will be available later. Interleukin 28B genotype, CC is favorable, TT is unfavorable, and CT is average.
With the CC genotype, a third drug might not even be needed and it may be possible to shorten treatment.
European guidelines indicate that with a favorable genotype, triple therapy isn't necessary.
There is data suggesting that if the patient has less than a 3 logarithm reduction in the 8th week, it's likely that he or she won't respond to treatment.

Termination due to adverse effects (SE) – 14% (practically identical with standard treatment). Common SEs for boceprevir – anemia. It's possible that to adjust the dosage, erythropoietin should be taken in the registration studies.
Anemia is more pronounced in triple therapy. Merck/MSD has provided erythropoietin absolutely free of charge in the registration studies.
Another study has been conducted: Group 1: the dose of ribavirin was reduced. Group 2: was given erythropoietin. Result: there was absolutely no difference with regard to effectiveness.
The registration research for boceprevir did not include patients with null response. A separate study, PROVIDE, was conducted in which null responders participated. They were given the chance to go through the triple therapy treatment course again (40% effectiveness).. There was a threefold increase in effectiveness when compared to the standard therapy (according to RESPOND-2 data).
Even if a patient has an unfavorable genotype, but responds early on, chances for successful treatment are high.
The data from the third phase is repeated exactly in clinical practice.

Question: Is a dose adjustment for ribavirin being used?

***Answer*:** Yes. Some people think that you need to keep the dose for ribavirin the same over the course of three months because of the drug's important antiviral effect. But there is a clinical opinion that nothing happens in terms of efficacy if the dose for ribavirin is adjusted.
Patients who stopped therapy during the lead-in period were 2% out of 100. The lead-in period helps identify patients who will not be able to withstand dual therapy. For these patients it makes sense to wait for the next generation of drugs.
Percent of people who stopped therapy in the 12th week due to ineffectiveness: 18%
Percent of people who stopped therapy due to adverse effects: 10%

<u>Taking the medication</u>: four capsules three times a day. A light snack is enough.

The overall effectiveness for the first genotype with a high adherence: 56-57% (according to data from a private clinic where patients themselves paid for treatment and where therefore the level of adherence was higher).
If the patient is not adhering to treatment, he is removed from treatment because of the risk of developing resistance.
If a patient is two hours late, it nonetheless makes sense to take the dose late.
If a patient is more than four hours late, it is better to take the next dose, although there are no specific guidelines on this issue.

Question: Where does post-marketing research take place?

***Answer*:** At the moment nowhere in EECA, and this is unlikely to change.

Question: Will there be a reduction in the frequency of taking boceprevir?

***Answer*:** It's unlikely to be reduced to two times a day. It might be possible to reduce the length of therapy to 24 weeks, if the patient is naive and if there is an early response.

Plans for the drug: research is being conducted with patients having a HIV co-infection.
Several studies are investigating drug-drug interaction (collaborative research).
Co-infection – two groups, 48 weeks of treatment, plus observation through the 72nd week, patients were naive but undergoing ARV.

Question: Will the observation period be extended?

***Answer*:** No. The observation period will be standard – 24 weeks.

1 case of therapy being discontinued due to issues of adherence – 1 person could not adjust to the regimen of taking the drugs three times a day.
SVR 12 – 60.7 had a co-infection on triple therapy.
For 7 patients it was not possible to control VL HIV.
Severe adverse side effects in the triple therapy group – 11 people. There is a letter that does not recommend the combined use of PI and boceprevir, excepting atazanavir.

Counter-indicative: Darunavir/r, fosamprenavir/r, lopinavir/r (ritonavir- boosted PI), efavirenz.
Combined use permitted: Truvada, atazanavir, maraviroc, NRTIs, raltegravir.

Drug-drug interactions (either when boceprevir is the victim or when it inhibits the effect of another drug):
With tenofovir it is possible that adjustments with methadone and byprenorphine will not be needed. It is NOT recommended to take together with boosted PI, it is possible to take with raltegravir.

Question: When will boceprevir become available in Central Asia?

***Answer*:** The product was approved in the USA two years ago, Delays in EECA are chiefly connected with registration.
143 patients received treatment under an early access program in EECA. Patients should be non-responders and they should have cirrhosis.

New drugs in the line:
Vaniprevir – MK-7009
Protease inhibitor NS3 – MK-5172
Inhibitor NS5A

Molecule 7009 – like boceprevir, it is taken with pegylated interferon and ribavirin.

Molecule MK-5172: one time per day, does not required boosting, effective against genotypes 1 and 3 (possible effectiveness against other genotypes). Multiple testing is planed in order to determine the optimal regime, as well as any drug-drug interactions.

Issues of access:

The developing world and emerging markets cover about 80% of the population that is infected with hepatitis C.
The World Hepatitis Alliance is working with WHO to prioritize hepatitis C. Work with governments is proceeding slowly. Hepatitis C is still not considered a priority. There is very little information about the disease incidence in countries south of the Sahara. It is unlikely that donor funding will be a factor in improving access to hepatitis C treatment. Unlike in HIV where many countries up until now relied on donor funding, for hepatitis C treatment, responsibility for funding will likely fall on local and national governments.
Priority patient group: those who received treatment earlier, null responders, relapsed patients.
In 2016-2017 or sometime thereafter, a non-interferon treatment may be available.
Merck/MSD is the only company that is currently manufacturing a complete course of treatment for hepatitis C. The company Roche holds a large portion of the market for pegylated interferon.
When planning access, it is necessary to take into account the model being used by the government for the for national health system and whether healthcare is provided through public or private health systems.

Question: Have the funds which Merck/MSD invested in developing pegylated interferon been returned? Why haven't you lowered the price over the last ten years if you have already recaptured the money spent on development?

***Answer*:** Pricing for pharmaceutical products is also related to new research. The profits from drugs today go for the development of new drugs today. Research and development of new pharmaceuticals is a very high risk business. Recently five products were removed from the third phase because of ineffectiveness. This cost the companies developing these medicines millions of dollars. You have to remember the specifics of the pharmaceutical industry: money is spent now, but the profit will only be realized in 15 years. We know that in a number of countries HCV treatment is not compensated. We need to find a balance between profits on investment, the cost of future research, and access to treatment. Not all governments will be able to equally offset the cost of treatment. The solution is differentiated pricing structures within countries and across countries. We are working on strategies to make this possible. One approach is volume based pricing. Another strategy is a guaranteed treatment duration. We could consider an approach where payment is made for a fixed duration of treatment and then there would be no extra charge if additional treatment were needed. For example, the lead-in period would be free, thereafter it would be possible to estimate the chances of success. If these chances are low, the lead-in period would be free. We also want to create a dossier that, from the point of view of science and economics, will convince the government to buy more courses of treatment. In Scotland, research showed that treating people now saves money in the future because this reduces the number of viral infections. We, together with community groups, want to convince the governments that treating hepatitis will save them money. The company Roche, with its drug Pegasys, is the market leader (70-80%). We are trying to offer a competitive price. In this region, we see price equilibrium. More work needs to be done with the government, and we want to work together with you on this.
The merger of Merck/MSD and Schering Plough took place two years ago. Our philosophy at the Merck/MSD emphasizes working to enhance access to health and our medicines. We are

interested in dialogue with all of our stakeholders, including patient communities. I cannot comment on the topic of no dialogue for ten years.

Question: In Russia, the prices for Roche and for Merck/MSD are virtually identical. Sometimes it seems like the two companies have reached an agreement. Some people think that the companies aren't interested in dealing with the government, because they are completely happy just working in the commercial market.

***Answer*:** We are interested in working with the government because it is the major buyer, and clients themselves aren't always able to pay. We are not trying to say that there were cases with a significant reduction in price. The point is that Merck/MSD is trying to adopt a flexible approach to pricing. Suppose we offer a lower a price in one country or another, but this is when the factor of referential prices comes into play – it is important that we are able to ensure that the lower price for a country working to improve access to treatment is not then reference by a country, whose government isn't actively working to increase access to HCV treatment.
Given the small market share, we are trying to offer competitive pricing in comparison with Roche.

***Commentary*:** the GDP in Armenia is between $2,000 and $4,000. It is not logical to use countries like Scotland and the USA for comparison. I understand that you want to use us for discussions with the government, but you yourself don't want to do anything. In Armenia, cities are still in ruins, and to ask the government to provide treatment for HCV at reduced prices is just not possible.

Question: In light of the fact that the money spent on developing the drugs has long since been returned, please explain the company's pricing policy.

***Answer*:** We don't make account for the historical expenditures on research and development on a product when determining our current pricing for a medicine. The revenue from current medicines is what funds the research and development of future medicines, which includes research projects that turn out to be unsuccessful. This conceptualization of return on an investment is not how we determine pricing for a medicine. We are willing to employ a differentiated pricing policy to increase access to medicines based on public health need and countries' levels of economic development. Look at Egypt and Thailand – their governments have really tried to increase access to treatment. In addition, peginterferons are biological products and they are more expensive than pharmacotherapy.

***Commentary*:** It is amusing that Russia and Egypt have been placed together in the same zone of reference. In Egypt, the price is 2,000. In Russia, it's 15,000.

Question: Are there any plans to localize production?

***Answer*:** It's not a necessarily true that localized production results in a reduction in price. There are many other factors that influence the price.

***Commentary*:** Localized production is important, because in Egypt, the price was reduced after a compulsory license was issued and production localized. [Note: a compulsory license was not issued for PegIntron in Egypt. There is a local generic peg-INF in Egypt.]

Question: In light of the introduction of boceprevir onto the market and the increase in the cost of treatment in general, how does the company plan to increase access, maybe by sharply reducing the price for interferons?

***Answer*:** A differentiated pricing policy, possibly a package price for the course of treatment.

Question: Is it possible to use the decision to reduce the price in Georgia to $148 as a precedent for other countries?

***Answer*:** Global Fund tenders – that's flexibility that we can make use of in order to improve access. We are open to discussion. However, it's important to remember that different payers work with different segments of the population. The price for the Georgian Federation is a special one.

Question: Many companies are working on new drugs and in a few years they will become available. Does this have an effect on the price? Can you specify the cost price of pegylated interferon?

***Answer*:** The cost price is confidential information. As to the future, the combination peg/rib (+ direct agent) will be standard for the next three to four years. Then the market might change.

Question: There are only several countries that can afford treatment, the rest can't. Would it be possible to use a mechanism of voluntary or compulsory licensing of biosimilar drugs?

***Answer*:** Merck/MSD works to enhance access to our medicines through multiple mechanisms, including through differential pricing frameworks which take into consideration countries' level of economic development and public health need and differentiates between public and private markets. I am very pleased with the discussion that we are having today. It's really too bad that despite all of our efforts, governments do not prioritize treatment for hepatitis C and that there still isn't enough access to treatment. We must work together. We need to implement strategies so countries with fewer resources and higher public health need pay less and that countries with greater resources pay more and so that governments will prioritize treatment of hepatitis C in national health programs.
In any case, the governments should pay for the consequences of lack of treatment. Dialogue is very important. We probably need to convey to the government how health care expenditures can be reduced with the help of our products.

Question: Do you have plans to grant voluntary licenses to generic companies?

***Answer*:** No, at this point in time do not have any such plans.

Question: What do you think of compulsory licensing?

***Answer*:** We support the flexibility of TRIPS, we are in agreement with the provisions for emergency situations. However, these provisions should not be abused. And it is also important to remember that pegintron is a biological product. It is important to ensure that biosimilar products have gone through the necessary clinical and requlatory approvals.

***Commentary*:** People are dying. That's a universal loss, but your loss is in dollars.

Question: You spoke about differentiated pricing depending upon burden and upon the capacity to pay. Why don't you approach pricing from the point of the cost of production?

***Answer*:** What is most important to us is that patients get the treatment they need. Just like you, we do not want any patients to die. We are investing in new forms of treatment, and for us boceprevir is a step in that direction. It's not a breakthrough, but it is one of the steps. As for local production, we are willing to discuss with governments and companies on a case by case basis where this might

be appropriate, but local production in itself is not the solution to the problem of access to drugs. The solution to the problem is the government's position with regard to the treatment of patients. We are ready to work with governments, if they are ready to accept national treatment programs.

***Commentary*:** Once again, it is necessary to emphasize the necessity of working with people, and not just with the health care system, but this is only possible if prices are reduced.

***Commentary*:** Take a look at the small countries (for instance, Moldavia) in terms of localizing production.

Question: A certain Ukrainian company has started to manufacture generic peginterferon. They are planning to cut the price of the original Roche product by 2-3%. Do you have any plans to bid in the Ukraine?

***Answer*:** We are considering different options in the region.

***Conclusion*:** It is a positive thing that we have started a dialogue. We listened to Merck/MSD's position, which takes into account the interest of its shareholders. We likewise want Merck/MSD to hear our position with regard to people who do not have access to treatment, either old or new. You can't just talk, you can't just wait for the catastrophe, you need to prevent it. According to our data, the majority of governments do not have the will power, and given the current prices, there won't be any breakthrough. Even Russia's budget can't handle it. Therefore, the question of lowering the prices must be addressed.

The position of the community of patients was read.

End of the meeting.