[00:09:57]

Małgorzata Siewierska: Welcome to the Celon Pharma Capital Markets Day.

[00:10:00]

My name is Małgosia Siewierska and I am head of investor relations in the company. Today, we are going to give you a helicopter view on our company's operations. Let me introduce you to our today's agenda. Our meeting is divided into three main parts. First, comes the corporate session with business and innovation operations and financial highlights. Then we will move to the KOL session to discuss the most important unmet medical needs into three therapeutic areas: neuropsychiatry, oncology and inflammatory diseases. At the end, we invite you to participate in the Q&A session, but feel free to share with us your comments and thoughts during the whole meeting.

[00:10:54]

At any moment, please use the chat below the stream, which is available at our website. Now it's time to introduce you to our today speakers from the company's side, executive board members: Maciej Wieczorek, CEO, Jacek Glinka CCO and Iwona Giedronowicz, CFO; KOL session will be hosted by Piotr Wierzbiński, a psychiatrist, and his guest in this section will be Professor Eduard Vieta from the University of Barcelona, Professor Jair Soares from University of Texas...

[00:11:37]

...and Professor Joanna Chorostowska-Wynimko, National Institute of Tuberculosis and Lung Diseases in Warsaw. And finally, I would like to add that the presentation you are about to hear has been prepared by the company solely to provide you with general information of the company and its group and an overview of its operations. This presentation is provided for informational purposes only and does not constitute an offer to sell or subscribe for securities. This presentation should not form the basis of any investment decision and you should reach your own conclusions before making any such decision.

[00:12:25]

Now, I would like to invite Maciej Wieczorek to start the corporate session.

Maciej Wieczorek: Good morning and good evening. It's a pleasure for me that you are with us today during our first capital markets day.

[00:12:54]

My name is Maciej Wieczorek and I'm the founder, the CEO of the Celon Pharma company. I founded this business almost 20 years ago at the times where generic products represented a great business opportunity. Benefiting from patent cliffs and not yet fully incorporated savings potential from generic

products. But from the very beginning, it was my dream to be in the innovative business, and I wanted to, in fact, in the last two decades, these values for the entire company.

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So, we started almost 20 years ago as a generic business with first few products introduced to the market, and starting from 2006, we started our first R&D department.

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We benefited from Poland joining the EU and with that, we managed to co-finance our research and innovative program significantly. So today, most of our R&D programs are co-financed from EU funds. We have moved with our innovative pipeline and in the years 2010-2014, we entered with the first few compounds into preclinical and toxicology programs.

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At the same time, we didn't forget about generic business, that is for us a cash generator, but we moved into more complex generic products using sophisticated respiratory delivery with a particular focus on dry powder inhalation. And, with this technology, we have introduced our first product, Salmex, today our major growth driver. It was introduced in 2013 on the market and we have approved this product into many more European and out-of-European markets. So today, our major focus, more than 90 percent resources, go into innovation.

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We have several programs in both preclinical and clinical development, and five of them is in clinical development.

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To summarize our strategy, we have started from generic products. Relatively easy to manufacture and develop and we move into innovation, innovative programs.

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At the beginning, in the innovative pipeline, we use small molecules. And we are expert now in many technologies using small molecules, we have a very experienced medicine and chemistry team.

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~~That's.~~ We are now moving more and we are using new technologies in designing our products, our drugs, and these are recombinant proteins by specifics and RNA technologies. And finally, we wanted to

escape from being simply an early product or early technology supplier, into, given our more and more expertise in commercialization and product development, into being for selective products and selective indications marketer on the selective global markets. So, all of this strategy is based to increase, to add the value to the shareholders. So, we are on the verge of accelerated growth. We benefit from the competencies we have developed, both in commercialization of our branded generics and our discovery and development experience we have gained up to now. We know how to design our products to target unmet medical needs, and we look for products with blockbuster potential.

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Later, you can see that each of our product has the blockbuster status, aiming between one to five billion sales – big sales. We are positioning our programs to have to be best-in-class properties. And all of that can be achieved with very solid clinical development, so we are with five of our programs today in clinical stage and we have first very robust readouts from our clinical program. And you can expect in the next couple of years to have more and more clinical readouts from phase two and, likely, phase three.

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The programs are designed to show clinical benefits, real clinical benefits for our patients.

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So, we have a very broad late-stage clinical program in the next few years.

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Let's move about our key goals in the next five years. So, our focus is innovation. We want to increase our R&D spending, to double it, with the next few years. Numerically, we want to advance at least two products per year into clinical development and advance at least two products into pivotal stage, phase three development. Our full carry dry powder is ketamine, we expect to be approved in the next few years in the major markets, U.S. and EU, and we'll do that with our partners. We target to sign commercial agreements this year.

Z komentarzem [R1]: Fragment nieczytelny

[00:19:48]

We also target for two, at least two significant partnership agreements in the next few years for our other programs. We don't forget about our branded generic business, we want to expand that based on Salmex's success, and we have the plan for continuation of our geographical expansion. We have two markets that we think about, that is China and the US, and we have the plan, strategy for each of these markets to develop and launch our products, Salmex product, in the next few years.

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So, with all of that, we expect significant double digit annual growth after 2025. We'll add some fuel into jet branded generics by adding a few products in respiratory and neuropsychiatric field in the next few years.

[00:21:01]

Jacek, please, your turn for the generics.

Jacek Glinka: Thank you Maciej. My name is Jacek Glinka, I am responsible for commercial affairs and business development at Celon. Before that, I spent more or less half of my previous professional life in the consulting industry. And then I moved, I switched sides. I moved to the pharmaceutical industry where I spent around 11 years with Polpharma, the largest pharmaceutical company in the capacity mostly of the CEO. And then I moved to Mylan, where I spent six years as president for Europe, at the same time being also responsible for leading the medicines for Europe, formerly known as the European Generics Association, in the role of president and vice president.

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Today, it's my pleasure to walk you through the generics business quickly, because the focus of today is mostly on innovation. But generic business has built a Celon foundation to move into innovation. We started with the focused approach on the Polish market, which was branded generic market at that time, where we have launched a few first-to-market, important molecules. And subsequently in 2013, with development of Salmex, we have moved to the overseas markets. And today, Salmex is our most important product, being responsible for around three quarters of the sales, which totaled last year around 130 million zloty.

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Our approach to commercialization is different for the local market and the different for the overseas territories. In Poland, we have developed full commercial infrastructure to support our business with excellent coverage of physicians in relative therapeutical areas, as well as stronger marketing function, thanks to that, you could see that our market share puts us in the leading position in the relevant therapeutical areas, ranging from 8 to 64 percent for our second largest brand and 39 percent for our key brand – Salmex. In the overseas territories, so we have a different approach, we are working exclusively through the business partners who have relevant strength in the relevant markets, such as Mylan or Glenmark.

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We have started commercialization of Salmex in 2013 with the registration in Poland. Subsequently, we have moved to most important European markets and, thereafter, to the rest of the world. Today, we market this product in more than 20 countries. In another 20 plus countries, we are in the process of

registration, which means that we have created the first truly global product of the Polish pharmaceutical industry. Our export sales dropped a little in 2019. This was caused by the legal dispute with Glaxo over the intellectual property rights to Salmex, which has concluded with the settlement agreement in the first quarter of 2020 and since then, our export sales started to grow 300 percent year-on-year last year and have achieved around 35 million Polish zloty or 10 million US dollars. Indeed, we want to continue our geographical expansion with this product. We are expecting a double digit CAGR in the next years to come. Our generic business is virtually vertically integrated. We have built the manufacturing and development capabilities in-house. As a result, all our generic products are manufactured internally.

Z komentarzem [R2]: Nie jesteśmy pewni, czy założeniem była właśnie zbitka tych słów, czy mówca się zająknął i intencją było „is vertically integrated"

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And we have today, after the upscaling programs built more than sufficient capacities to support current and future volume of demand. So, with this, we have been able over the last 20 years to develop many important strategic competencies, such as pharmaceutical development of different forms, such as management of intellectual property and also GMP manufacturing for different dry forms, as well as dry powder inhalers, which we are manufacturing in-house. It was also interesting for us with Salmex to learn about global regulatory landscape, as well as build the global supply chain.

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And finally, we have built the commercial infrastructure, both branded infrastructure in Poland, as well as a network of different business partnerships around the globe, that today not only support our generic business segment, but also build a foundation that is critical to support certain innovative programs. So, with this, I'm asking Maciej back on stage to talk about the most important part of our business, which is innovation.

Maciej Wieczorek: Thank you very much, Jacek. So, I'm going to show you the innovative business update, to present you this update.

[00:27:27]

So let me start with the highlights where we are in which to appeal to areas, we are in this innovative business. And we are in the same areas where we started our branded generics many, many years ago. So we built competencies today, which are supported by teams of between 30 to 60 researchers and scientists in these special therapeutic areas. And these areas resulted in several preclinical and clinical assets with five clinical programs that I want to discuss in more detail today. So let me start first with the most advanced assets.

[00:28:19]

This is our Falkieri. Esketamine in dry-powder inhaler, the program that has just completed phase two. And we have very good, excellent, phase 2 readouts from our bipolar depression study, and this is our

major indication that we want to move this agent forward, however, unipolar depression indication, the same as for Spravato, is also under evaluation.

[00:28:54]

We have the first of our agents in neuropsychiatry, this a small molecule called CPL 36, and we designed this molecule to improve on shortcomings of first-generation PDE10a inhibitors. And later, I will show you that we have the molecule that has a very clear best-in-class profile. So, we are running two phase two studies in schizophrenia and Parkinson's disease, levodopa-induced dyskinesia.

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In metabolic diseases, we have just completed phase 1 of our small molecule, GPR40 agonist. Many years ago, the molecular target was high expectations in diabetes type 2, but due to toxicity of first generation agents, most of these programs were terminated. So, we discovered a molecule that have have improved on these shortcomings of first-generation of GPR40 agonist, and this is CPL280. This molecule, we are just preparing to move it into phase 2 in these two indications, the one is diabetes type 2, and the second is diabetic neuropathy.

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In oncology, we have the first targeted agent, the CPL110, and our CPL 110 is a small molecule that is a FGFR inhibitor.

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This is a very hot area in oncology and we have very robust efficacy data of these inhibitors in many solid tumors. So, we believe our inhibitor to have very good biodistribution properties. We'll share significant market share in this attractive disease, in these attractive markets. In inflammatory diseases, we have the first in class dual JAK/ROCK inhibitor that is in phase 1 and this is also a very attractive asset that will be the topic for discussion with our key opinion leader.

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So, let's move to Falkieri, as I said, we are very happy and very excited with phase two bipolar depression readouts we have on hand.

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But first of all, we want to show you that we have clear different season, different profile, for Falkieri. The first agent approved, to first product approved was esketamine, that is called Spravato from J&J. First of all, we use different administration.

Z komentarzem [R3]: Słyszymy season, pytanie, czy takie było zamierzenie?

[00:32:00]

We use dry powder, pulmonary administration. And with this administration, we consistently see much more predictable pharmacokinetics, so these more predictable pharmacokinetics can translate into more precise dosing and potentially can translate into better, tolerable agents.

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And our very initial readouts from phase 2 may suggest that particular in bipolar depression, respiratory administration is giving a very good, very clean safety profile. So, as I said, we are developing our molecule and this was a little bit risky approach, but an approach that today give us to be on the leader position, because we hypothesize that esketamine can be effective and safe in bipolar depression and bipolar depression, as we know, is consisting of manic phase, psychotic phase and depressive phase, so psychometric agents like ketamine, esketamine, theoretically, may induce mania, may increase the risk of psychotic state of the patient with exacerbation of mania.

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So, it was some kind of risk, but later today, during our key opinion session, you will see that we are not inducing mania. We are even improving mania in the course of the treatment.

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So this is new data, very impressive data, which position this molecule in treatment-resistant bipolar depression as, potentially the agent of choice, of course, provided that we can replicate our phase 2 readouts into phase 3 studies. So, we have completed two phase 2 studies with bipolar depression, having very robust efficacy and very good safety data.

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There is one more difference between our development, Falkieri, compared to Spravato.

Z komentarzem [R4]: To nie wybrzmiało, a jest ważne dla logiki zdania

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We are incorporating to our inhaler some electronic device that ultimately, and this will be in the life cycle of this product, may give us chances to have enough of this product in the home setting by self-administration of patients in a maintenance treatment of the disease.

Z komentarzem [R5]: Fragment nieczytelny – czy chodziło o enough? Prośba o weryfikację, ponieważ wówczas to się „nie składa” logicznie.

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So, if we get that, we'll have a real huge competitive advantage over the other ketamine or esketamine administration that must be used both acutely and chronically in the clinics.

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So, we are working on that. And later, in developments in clinical development, we are going to show you this data.

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Let me come back to the rationale behind this product development; so you know that we have huge expertise in respiratory technologies, so we leverage on that in designing and developing our Falkieri device, we achieve very high, long deposition efficiency.

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And it means that a large part of the drug is administered to the lungs, not gastrointestinal track. Not other parts of the body, but to the lungs, where absorption takes place; and we achieve efficiency of lung deposition around 50 percent and today industry standard is around 20, 30 percent. We achieved that with consistent delivery. So with these CMC and product development strong data, we started phase 1 in healthy volunteers and on this slide you can see our PK profile.

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And this profile shows us that we achieve the same drug plasma exposure using much lower nominal doses. So, it means that our product has higher bioavailability and we calculated that; we have higher availability in comparison to intranasal Spravato formulation between 30 to 45 percent. So, of course, that's good because it means better safety. We can also see much lower inter subject variability. So, again, it may translate into a better safety profile.

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We have first, with this phase 1 and good safety profile, we initiated two proof-of-concept phase 2 studies, one in treatment-resistant unipolar depression, and the second in a new indication, not yet touched by anybody, in treatment resistant bipolar depression. In treatment-resistant, unipolar depression, we could see some signal of efficacy, mostly pronounced at the highest dose, but we didn't achieve statistical significance. However, in treatment resistant bipolar depression, we had very robust efficacy data with the primary endpoints to be statistically significant and clinically meaningful; we achieve efficacies of around between 0.8 to 1.4, this is large to very large. For me, not yet seen in any bipolar depression studies.

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We can see also some better safety profile in bipolar depression study in comparison to unipolar depression study, our study, but also when we indirectly compare our safety data to what can be seen in TRANSFORM-2 Spravato phase 3 studies. So bipolar depression is our major indication and we move as the first indication. We move forward with this indication. So, this is also a very attractive indication. It

is less prevalent, but later today, I think our expert will discuss a real prevalence that is much higher than statistics say.

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So many more patients have bipolar depression, then are diagnosed, we have very few approved treatments in bipolar depression and we have only four antipsychotics approved in US and one in EU.

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Of course, psychiatrists treat bipolar depression that is a highly debilitating disease with many different class of drugs, particularly they use anticonvulsant drugs, but for sure this is the setting, clinical setting with huge unmet need, and there are no added modality that showed consistent effect in treatment resistant setting. And we can see the peak sales of our product in this setting in treatment resistant bipolar depression that was estimated by an independent research company to be around USD 1.3 billion. That is almost double this peak sales of our product in unipolar depression.

Z komentarzem [R6]: Fragment nieczytelny – prosba o weryfikację

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This setting has much more therapeutic options. We have approved more than 30 antidepressants in different classes in these treatment and antidepressants, albeit slowly, but work in majority of patients.

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And of course, we have Spravato approved in this indication. So, we expect Spravato to be a market leader in unipolar depression for the many, many years from now.

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So let's move to the second phase 2 agent. This is phosphodiesterase 10A inhibitor and again, we had the first generation compounds that delivered mixed results from phase 2. The closest to achieve statistical significance in schizophrenia were compound from Takeda called TAK063. However, today we know more and more about the pharmacodynamics of phosphodiesterase 10A inhibitor. So we believe our agents bypass the limitations and drawbacks of first generation agents and I will show you why we believe that is.

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First of all, our molecule is chemically different to both MP10 from Pfizer and TAK063. It has superior pharmacodynamic profile and today it means that we should have very fast off from the enzyme. And when we compare dissociation from the enzyme – and this is the table on the right – you can see our agent has few to several times faster dissociation from the enzyme.

Z komentarzem [R7]: Fragment nieczytelny – może skrót myślowy?. Rozumiemy, że chodzi o „fastest dissociation”

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And with that, the agent's inhibition of phosphodiesterase 10A is focusing on the indirect pathway responsible for antipsychotic effect.

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And if we are for too long binding to the enzyme, we can start signaling off direct pathway and compensate this antipsychotic effect; so our agent with this pharmacodynamic profile is best in class. It has the fastest dissociation from the enzyme.

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No wonder we can see much more robust preclinical efficacy and safety profile in almost all animal studies that we test, and we compare our CPL36 with both Takeda and MP10 compounds. Of course, the general expectation from the class of these drugs, it's no metabolic or hyper plaque anemia risk – today, the major limitations for chronic long term use of antipsychotics. And also, we have phase I in healthy volunteers, so this phase one, again, give us very good pharmacokinetic profile. And here on the left, you have two figures showing our pharmacokinetics to be linear, and the tested doses between 1 to 60 mg.

Z komentarzem [R8]: Ze slajdu wynika 60, ale brzmi jak 16 – prośba o weryfikację dla pewności

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And it's after day 1, day 7 and day 14, we achieve after one daily administration, the plateau of the exposure to be at around day 4. And with a dose 40 milligram per patient once daily we achieved the exposure, the AUC to be around of six thousand, six-fold greater then was achieved by Takeda compound at the nominal dose 20 milligram, the dose tested in phase 2.

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So we believe we can move up to ceiling with the exposure, with the target inhibition, not yet tested by any first generation PDE10A inhibitor. And one of the reason why that was is because Takeda and also MP10 are indeed pharmacokinetically imperfect.

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So you can see in non-linear pharmacokinetics and when you add the dose more than 30 to 40 mg, you have the plateau of drug exposure and some side effects were also presented with the higher doses. So I think this PK profile with our molecule is superior and it can add the confidence that we can see the effect in our face, the proof-of-concept studies.

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So we started two of such studies, one in acute schizophrenia in around 165 patients, we test two doses, 20 milligram and 40 milligram, once daily. We administered for four weeks with the PANSS positive subscale as the primary endpoint at week four. And the second study, not yet tested by any company, is levodopa-induced dyskinesia in Parkinson's disease. So, we are planning to randomize around 110 patients at two doses, 20 and 40 mg, again, administer our product once weekly for four weeks, whereas the primary endpoint is to be Unified Dyskinesia Rating Scale at week two. The readouts from both studies should be available in the first half of next year. Let's talk about the markets; of course, schizophrenia's a huge market, but we are treating patients with generic products.

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The new market is still in very, very, very sizable. In volume terms, it's around 10 billion dollars. It's mostly driven by a few agents still under patents, or extended release forms; I know some delivery systems that are used to increase the convenience for the patients. It is a very, very undertreated disease and still lots of poorly addressed parts or domains of this disease.

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So, these are negative and cognitive symptoms, but also almost all of our typical antipsychotics today used carry some tolerability issues with weight gain, with metabolic impairments or with movement disorders. So once we have the product that is at least similarly effective to the currently used antipsychotics and free from the side effects, we believe it will have lots of advantages on the market and grab significant market share. Levodopa-induced dyskinesia is a disease with even more unmet medical needs, so we are using mostly amantadine here, generic amantadine.

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There are some proprietary extended release formulations, but more than 90 percent of the prescriptions come from generic amantadine. So the market is huge, around half of patients after 10 years of levodopa administration, present these side effects and levodopa today is the gold standard. I cannot imagine and neurologists or psychiatrists cannot imagine to change that, to substitute that with another drug, because, simply, levodopa is very effective.

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But these dyskinesias that are starting after a few years are something that will constitute a real, therapeutic challenge.

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So this is a very attractive area. And today there are a few other companies that have phase 2 other programs. So let's go to metabolic diseases and our most advanced program.

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And as I said, this is a very attractive, novel, GPR40 agonist for all of you that are in diabetes.

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You probably remember a few years ago, GPR40 had high expectations as a new class of drugs.

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It has a very simple mechanism of action, very similar to sulfonylureas. It releases insulin – contrary to sulfonylureas – that release insulin independent of the glucose level. We have the glucose-dependent insulin release when GPR40 agonists are used. So with this property, we can see consistently much less hypoglycemia risk. And this is a nightmare when using sulfonylureas, very effective agents, but associated with several percent of the hypoglycemia risk that sometimes may be even fatal.

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So the rationale to develop GPR40 agonist was to deliver an agent with the very simple mechanism with the release of insulin, but without this hypoglycemia risk. However, the first generation molecules were found to be hepatotoxic. And for many years, we didn't know why they were hepatotoxic. Today, we know that this is the combination of the very strong bile acid transporters inhibition and also some biodistribution, particularly for fasiglifam.

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So when we compare the most important properties with our agents to the properties that are responsible for the liver injury risk, we can see in each of the property that we are on the safe side.

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We have an order of magnitude lower inhibition of bile acid transporters measured by IC50. On the left is our molecule. On the right is fasiglifam. The highest value is better.

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And we have also different, better biodistribution and this is the central figure, you can see that our molecule has the exposure in plasma, mostly, not liver, in contrary to fasiglifam, that is accumulated in the liver.

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So, inhibiting of bile acid transporters with this very high liver concentration then result in this hepatotoxicity risk. We are also much safer on almost all of the hepatocytes.

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So this has given us a very confident picture from the cell and ex vivo experiments that we should be safe when we analyze hepatotoxicity risk.

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And this was supported in animal studies, in toxicology studies and also in our phase 1 program that has the special focus on liver enzymes, bilirubin and other hepatotoxic risk parameters. So we don't see any receptor signals here in our phase 1 program.

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Of course, it's still small studies with few weeks of drug administration, but we must remember that for the fasiglifam we could see the ALT and AST increased levels in around four to five percent of patients, and these increases started early after administration. So it's really good we cannot see any of that in our preclinical high-dose tox studies and also phase 1 study.

Z komentarzem [R9]: Do potwierdzenia, czy nie chodzi o 45%

[00:53:02]

So we move this agent forward into diabetes type II and the indication that is completely new; and we are the first company to show with these GPR40 or our agonists to be effective in diabetic neuropathy. So where we are from the market point of view, of course, diabetes type II is a huge market, but at the same time we have many therapeutic options. We have two stars. This is GLP1 and SGLT2. And these agents are effective. They have some safety issues, but they have something that is now very important.

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It is called benefits beyond glucose control. And when we talk with the endocrinologists and physicians that treat diabetes, all of them say “Sulfonylureas are great agents, they are very effective, but there is hypoglycemia risk and we know that, and there is some weight gain risk, the patients on average have two to three kgs of weight gain; and at the end, particularly with the introduction of GLP1 and SGLT2, sulfonylureas don't have this benefit beyond glucose control.

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Of course, we know that most of sulfonylureas are generic products, so there aren’t any incentives for these companies to invest heavily into the programs, large clinical programs to show the evidence of that.

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Maybe there are, but our molecule is perfectly fit because it addresses all of the side effects and challenges with sulfonylureas. It has a very plastic mechanism of action. And it would be, we believe, very easy to convince physicians to prescribe our drugs because they'll be simply much better than sulfonylureas not carrying the risk and, you know, leveraging on the effect of insulin release that they remember from sulfonylureas.

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So we believe our agents have the chance to substitute sulfonylureas and this is still a very large market. It's not as large and with not as much potential as GLP1 one or SGLT2, but today, around seven billion dollars are spent on sulfonylureas. The markets of sulfonylureas is not growing much, but this is mostly because, as I said, there are newer agents with these benefits beyond glucose control and with our diabetic neuropathy indication. We think that this may be a benefit that can give us very clear positioning of our product in patients having inadequate control after metformin and presenting diabetic neuropathy.

[00:56:08]

So, let's move to oncology and in oncology, we have the first FGFR inhibitor targeted agent that would develop in gastric, bladder and squamous non-small cell lung cancer. Today, this product and its environment will be discussed in detail with our key opinion leader, Professor Chorostowska. So I'm going to highlight to you where we are with this program.

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So, first of all, this is a very attractive, hot area, and we have recently learned about clinical evidence of first agents in different tumors. So we are in phase 1.1.B, and we want to move into phase 2 next year with this agent.

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We target gastric, bladder and non-small cell lung squamous cancer. And these are huge tumors, with huge unmet needs. However, the market landscape is a little bit changing in bladder cancer due to immunotherapy. And immunotherapy today, mostly PDL1, we observed the response rate in advanced metastatic setting of around 20-25 percent.

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That is lower for Erdafitinib JNJ-inhibitor, that show response rate of 35 percent. So whilst you have the good preselected patients having genetic aberrations of FGFR, as you can see, you can achieve a huge response rate. So we have also a very early phase 2 study in gastric cancer with the monoclonal antibody targeting FGFR. And this antibody showed the benefit that was increase when the patients presented

Z komentarzem [R10]: Czy chodziło o 35? Brzmiało trochę jak „thirty-few”

more overexpression of FGFR2 kinase receptor. So it's again giving us some confidence that good preselection of patients, but patients that can respond to the treatment, may yield with the excellent clinical benefits.

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Non-small cell lung cancer is very attractive, and we know it's one of the most prevalent tumor. However, we are targeting squamous histology that is presented in around 20 percent of patients. And we see genetic aberrations of FGFR in non-small cell lung squamous cancer in around 20 percent of patients.

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So we are targeting the market of potentially a few billion dollars. So this is the last of our clinical stage assets, and this is a very attractive molecule, is a first-in-class dual JAK/ROCK inhibitor that was designed to have both anti-inflammatory and anti-fibrotic properties. And JAK inhibitors are well known today and we see the growth of these molecules. They are in many autoimmune diseases, show a very robust effect, similar to many biologicals like TNF Alpha, but all of them are probably related to some of the risk and we know about tofacitinib to have this risk, cardiovascular risk. We also know that patients with autoimmune disease, almost all of autoimmune disease are at excessive cardiovascular risk, this risk is increased by 30 to 70 percent. So it would be great to have an effective anti-inflammatory agent with the CV protection property and drug kinesis is well validated CV protection target. We know this is the one of the one of the mechanism that is used by statins and offers cardiovascular protection.

[01:00:18]

We know the agents that target ROCK has beneficial cardiovascular protection properties.

[01:00:24]

So we designed our molecule to have both these dual inhibition and we target many autoimmune diseases, these simple diseases like psoriasis or RA, but in patients with increased cardiovascular risk; we could also see the potential of this molecule in autoimmune diseases that require both anti-inflammatory and anti-fibrotic activity.

[01:00:52]

And this is idiopathic pulmonary fibrosis, pulmonary arterial hypertension, or interstitial lung disease in the course of many autoimmune diseases with a special focus on RA. So very attractive agents with many potential clinical settings, first-in-class, and we go forward with this agent. We expect in the next two to three months to initiate many phase 2 proof-of-concept studies in these indications. So let me start with plaque psoriasis. We know it's a huge market to take, quite well served by interleukin 17 and interleukin 27 monoclonal antibodies.

[01:01:36]

But at the same time, we know that there is a moderately effective Otezla that has the market size of around three billion. And this is the only oral agent approved in psoriasis. So we think that there is a huge need to have the efficacy better than Otezla and be administered orally to grab a significant part of this market. In RA, we are mostly focusing on RA with interstitial lung disease and we know several percent of patients are presenting this interstitial lung disease.

[01:02:11]

So, we think that this is a very attractive market. We know JAK inhibitors are doing well in this market and the market size of JAK inhibitors in RA today is around three billion dollars, with the expectations to grow to seven billion in the next couple of years.

[01:02:32]

And finally, we have two indications, very attractive. This is idiopathic pulmonary fibrosis. We know that there are two agents approved today. This is Esbriet and this is Ofev and the market size of around three billion dollars and growing.

[01:02:54]

And we have pulmonary arterial hypertension, again, very large market, seven billion dollars, very well served, but still with many agents, but still there are more combinations now under development. And there is room for other effective drugs in pulmonary artery hypertension.

[01:03:18]

These two diseases, IPF and PAH, are diseases with a very bad prognosis. It has not changed much, life expectations to be around three to five years, once the patient is diagnosed with this disease.

[01:03:39]

So this is our clinical trials news flow and, as you can see, we are going to announce to you many readouts from our phase 1 and phase 2 in the next quarters, we are just finishing Falkieri, treatment-resistant bipolar depression, longer term observation results. We are preparing Falkieri briefing package and go to both FDA and EMA and ask for phase 3 program.

[01:04:15]

With GPR40. this quarter, we will start our phase 2 in diabetes and next quarter in diabetic neuropathy. In CPL 116, in the next quarter, we plan to initiate a few proof-of-concept studies. And next year, you should see readouts from our PDE10a, JAK/ROCK and we'll initiate our FGFR phase 2 program.

[01:04:47]

So, every quarter, you should see from as many news from our clinical pipeline. So, we are really on the verge of accelerated growth and we leverage on competencies.

[01:05:09]

We had so far in both commercialization of our branded generics, but also we know how to design and develop the molecules that are properly selected for unmet medical needs, and we are trying to have best-in-class profile of our molecules.

[01:05:32]

All of that is tested in well-designed clinical studies that should show real clinical benefits for our patients, so we have a very broad pipeline and we expect to have impressive results from this pipeline, at least for some of our programs in the next years.

[01:06:22]

Iwona Giedronowicz: Good afternoon. My name is Iwona Giedronowicz, and I'm the chief financial officer at Celon Pharma. At the beginning, I'd like to show you some key facts and figures related to the financial results. I would also like to mention that, as of the beginning of 2021, we are using international accounting standards, so the numbers I'm going to present reflect that and them. First, I want to describe Celon Pharma's financing model. With the revenue of over one hundred and forty eight million in 2020, the branded generics business has allowed us to invest in the very expensive, innovative business, as costs of R&D, only in 2020, came to almost 53 million. We are currently running 15 R&D projects with five in the clinical stage of development, and we have received government grants to fund all of them.

[01:07:34]

So far, we used almost a hundred million, but we have also been granted additional over 350 million in government subsidies, which will be used in the future. All of those are nondilutive and nonrefundable. During the last four years, we have spent over 200 million finalizing over 95 percent of the R&D center construction. However, we are not anticipating more large capital expenditure in the near future. We want to continue this model covering between 60 and 75 percent of the annual R&D costs by the grants and the generic business.

[01:08:33]

Next is the company operations, divided into the branded generics business and innovative business.

[01:08:41]

Here you have forward EV indicators: revenues, expenses and EBITDA. The brand generics sales EBIDTDA, which in 2020 came to over 55 million, compensated EBITDA loss from the innovation business. As you can see, the company is reinvesting the profits from the operation business to generate more profit in the future.

Z komentarzem [R11]: Prośba o potwierdzenie, fragment nieczytelny

[01:09:12]

Although we have a well running, balanced business, we are also aware of many problems; we want to lead more projects into the second stage of development and then to continue them in the third stage. All of this is very money consuming. Please note that the third stage of all of our project is not going to be supported by any subsidies. The following information is on profit and loss, the growing depreciation and amortization reflect how much has been invested in the last year.

[01:09:54]

The R&D costs reflect work in progress, and the export sales show strong growth. Moving on to the balance sheet, I'd like to point out that the great increase in the value of the tangible assets is due to the R&D center construction with its equipment. In 2020, we acquired a license that will allow us to increase our sales. Particularly in the export market. It has also led to an increase in current and noncurrent liabilities. At the end of 2020, those figures were 5.1 million and 24.8 million, respectively.

[01:10:52]

The decrease in the equity stake in other entities is due to the final assessment of Mabion on the stock market.

[01:11:02]

As you probably know, the situation has changed and the volume bounced back. The construction of the R&D center resulted in a decline in net cash flow from 144 million in 2018 to 80.5 million in 2020. At the end of my presentation, I'd like to emphasize that Celon Pharma's focus is on developing the R&D projects. We have a strong branded generics business, but going forward, we want to focus more and more on our innovation business.

[01:11:49.320]

Thank you very much, I pass the floor to Małgosia.

Małgorzata Siewierska: Thank you. Now we will move forward to the KOL session. This time, we will use the benefits of modern technologies to connect two parts of the globe and discuss the first therapeutic area planned for today. This part of the conversation was prerecorded just before our event, and the

interviews were conducted by Piotr Wierzbiński, a psychiatrist. And now it is my great pleasure to invite you for watching it. Piotr Wierzbiński and his first guest straight from Barcelona and Texas.

[01:12:52]

Piotr Wierzbiński: Welcome, ladies and gentlemen, my name is Piotr Wierzbiński. I'm a medical doctor and philosophy doctor and I am a psychiatrist. I have 16 years of experience in treating patients with various mental disorders. And I have a great pleasure to conduct a session with key opinion leaders of today's event, which, for me, is also a great scientific adventure. The leitmotif of our today's meeting will be to discuss the unmet medical needs in various therapeutic areas, including neuropsychiatry, which is a field that is particularly close to me.

[01:13:33]

We will also discuss issues in the area of oncology and inflammatory diseases.

[01:13:38]

Today, there is a huge dose of knowledge ahead of us and meeting with international experts. During the meeting, in addition to talking to experts, I will share with you the perspective that is the most important to me from the point of view of the existing unmet medical needs. So first of all, we start with neuropsychiatry, very exciting. It will be very exciting for us because I will show you that psychiatry could be incredible also for non-psychiatrists.

[01:14:24]

We have two distinguished guests on our board, Professor Eduard Vieta from University of Barcelona. Good afternoon, Professor Vieta.

Eduard Vieta: Thank you. I'm here to answer any questions.

Piotr Wierzbiński: And Professor Jair Soares from Houston, from University of Texas. Good afternoon, Professor Soares.

[01:14:46]

Jair Soares: Well, it is my pleasure to be able to participate in the recording today. I appreciate the invitation. Thanks for inviting me.

[01:14:54]

Piotr Wierzbiński: Now we will talk about psychiatry. We will talk about epidemiology, about treatment in psychiatry, especially, we focus on unipolar and bipolar disorders.

[01:15:08]

So, Professor Vieta, the first question to you is an important thing, I think, for every clinician. Given the lack reliable biomarkers in psychiatry, how do you diagnose depression in bipolar disorder, also given the times of pandemic?

Eduard Vieta: So, in the case of bipolar disorder, it is very complex to do the diagnosis in times of pandemic, but also out of the pandemic because we rely on the information that the patient and the family sometimes can give up, and this is subject to a lot of subjectivity from the physician who does the interview.

[01:15:57]

Piotr Wierzbiński: I totally agree with you, but there is growing evidence to suggest that bipolar disorder, depression, is underdiagnosed. What can you tell me about the real life prevalence of this condition?

Eduard Vieta: Yes, I think that bipolar disorder is extremely prevalent, even though I'm using them cross-sectionally, only one in eight depressions are officially bipolar. In fact, an important study is a British study and others done by these authors show that if you use the right screening tools at your confirmation, up to 50 percent of patients with depression could be considered bipolar.

[01:16:46]

So this means that this condition is extremely prevalent and that there are a lot of unmet needs, with regard to diagnosis and treatment as well.

[01:16:57]

Piotr Wierzbiński: OK, thank you Professor Vieta. Let's switch to Professor Soares. Professor Soares, I know that you are in Houston, in Houston, I'm sure that the weather is better than in Poland, but let's focus on our topic. So how do we define treatment-resistant depression and how do you define treatment-resistant bipolar depression? Because for me, it's very important question. As a clinician, I always have a problem with these patients. So what should be the optimal therapeutic approach in this setting?

[01:17:35]

Jair Soares: Well, most commonly defined as having failed a couple of different medications, you know, like give it for proper time and at the proper doses as well.

[01:17:48]

And for bipolar patients or patients where there is a risk they might be bipolar, you try not to use antidepressants. So usually what you do, you try to optimize the mood stabilizer, if there are on lithium, you adjust the dose or if they are like, well, on lamotrigine or some of the other typical antipsychotics; so treatment resistant is defined as having tried a couple of different treatments.

[01:18:15]

Sometimes antidepressants are on that list, you know, and then you have to do it carefully because there is a risk that may trigger a hypomanic or manic phase, as you know.

[01:18:29]

Piotr Wierzbiński: Thank you, Professor Soares, let's move quickly to Barcelona, everyone appreciates the very good Mediterranean weather in Barcelona. So, Professor Vieta. What is the main problem with how the bipolar depression is being treated nowadays?

[01:18:46]

Eduard Vieta: The main problem is that many doctors still [...] there's no paradigm for unipolar rage or for bipolar and then they are used to try to push the patient out of depression very quickly. But bipolars are like a pendulum. If you push from one side, then it goes to the other side and gets back even stronger on the other side.

Z komentarzem [R12]: Przerwa w połączeniu

[01:19:10]

Piotr Wierzbiński: So, we're flying to Houston. Professor Soares, one of the key advantages of esketamine is its speed of action. Do you see a place of this therapy in the bipolar depression setting? And how does it compare with what we have available right now?

[01:19:34]

Jair Soares: Very much so. That would be a major advance; the speed of action is very important because these medications we use now – it takes usually two or three weeks or longer. So, you know, something that works faster would be a very important improvement.

[01:19:50]

And primarily, if it is a treatment that the data shows that it's not increasing the chances of hypomania or mania, that would be a very good improvement upon what we have now.

[01:20:06]

Piotr Wierzbiński: OK, Professor Soares, so, can you give us your thoughts on Celon's phase 2 data that showed that esketamine inhalation has a significant positive impact in treatment-resistant bipolar depression, which obviously is the area of high unmet medical needs?

[01:20:26]

Jair Soares: Well, and then early data, you know, with phase 2 data showing that help with bipolar depression. That's very exciting.

[01:20:37.620]

Piotr Wierzbiński: Professor Soares, we clinicians know that treatment-resistant depression is the area of high unmet need. So seeing the study results being so strong, with effect size of up to 1.4 gives us hope that we may soon have a useful addition to our therapeutic toolbox. Would you have any other comments on the study design and how to interpret these results?

[01:21:09]

Jair Soares: Very true. And that's where, you know, the effect size you mentioned is very impressive, that these trials are always, you know, in comparison to what, the placebo, because for some studies, for whatever reason, the placebo rates can be high. You know, people responding to the placebo, so you want to show that your medication is added to that; it's not at the level that the placebo is. And the other concern is sometimes, you know, you just look at the numbers in this scale and let's say improvement in like one or two points of this scale.

Z komentarzem [R13]: Fragment nieczytelny

[01:21:42]

Is that really clinically meaningful?

[01:21:45]

That's why, you know, looking at the effect size is so important.

[01:21:50.100]

As you know, if you have a trial where the sample is so large, perhaps a trivial difference will end up showing up as a statistically significant. But it may not be clinically significant, but the phase 2 trial, the data that I've seen is very impressive. It's properly power and that effect size shows that it beats placebo by a very substantial margin. The tolerability looks good as well, and it is a big market in an area of unmet need for sure.

[01:22:27]

Piotr Wierzbiński: Ladies and gentlemen, we go back to Barcelona and we have an important question for Professor Vieta. Was it a surprise to you to see such good results for esketamine in a phase 2 study into treatment resistant bipolar depression?

[01:22:49]

Eduard Vieta: To be to be honest, it didn't come as a surprise to me because, as mentioned, I was already expecting very good results in bipolar depression. I think what was important was to make sure that the compound was equivalent to other forms of esketamine. And as far as this is accomplished, then, esketamine works, should work in bipolar depression. And this is why I think these positive results are very likely to be replicated in a phase 3 study.

[01:23:27]

Piotr Wierzbiński: So, given the excellent phase 2 study results for Falkieri – Falkieri is the trademark for respiratory esketamine; so, given the excellent phase 2 study results for Falkieri in bipolar depression, is there any neurobiological rationale why esketamine should be more efficacious in bipolar depression as compared with unipolar depression?

[01:23:57.930]

Eduard Vieta: Yes, I think that it is likely to be more effective in bipolar depression than unipolar. And the reason is that under the umbrella of unipolar depression, we have a mixture of conditions. ??? in general. But this is a bunch of people, some of them having a true neurobiological illness and others having adverse conditions in life disappointments and other problems, social problems that cause some suffering, of course, but which is biologically different. Whereas for bipolar depression, there is more homogeneity because we know that they all have been manic or hypomanic in the past and we know that their depressions have a strong neurobiological background.

Z komentarzem [R14]: Zakłócenie w połączeniu

[01:24:53]

So these people are not so likely to have placebo response, which, you know, depression and you are more likely to respond to a biological treatment such as esketamine, in my opinion.

[01:25:06]

Piotr Wierzbiński: Thank you both you for your excellent answer. But now that we have the phase 2 study results available, what would you be looking for in the phase 3 study in terms of how this drug works and how it is tolerated, especially given the risk of switching to mania or hypomania?

Eduard Vieta: I wouldn't be surprised if there were some switching and I wouldn't care if this is a small amount of patience because it happens with any treatment. What is really important is even though now the results are very good, what is really important is that the results are replicated in terms of efficacy and

speed of onset, because if there is some switching, OK, that's fine. It's not such a big deal, of course, I prefer if there is zero switching into mania. But the most important thing to me is that the efficacy and the speed of onset is replicated.

[01:26:14]

Piotr Wierzbiński: Professor Vieta, Professor Solares, thank you for your time and thank you for being today with us.

[01:26:20]

Jair Soares: Thank you so much.
Eduard Vieta: Thank you very much.

[01:26:22]

Piotr Wierzbiński: With me is Celon Pharma CEO and founder, Maciej Wieczorek Ph.D. And can you give us your thoughts about phase 2 study results in treatment-resistant bipolar depression?

[01:26:39]

Maciej Wieczorek: Thank you very much. So we had an introduction with high expectations of esketamine in bipolar depression, I hope we will deliver in our phase 2 proof-of-concept study. So to remind you, we have designed the study as a double-blind placebo-controlled study in around 90 patients. The patients were qualified, those who had inadequate response to at least two previous treatments. So we had both patients on antipsychotics and anticonvulsants, and the patients were treated with our Falkieri esketamine dry powder inhaler twice weekly, over two weeks. Our primary endpoint was MADRS improvement over the placebo at week two, and we randomized patients with both types of bipolar depression, type one, presenting mania and type two, presenting hypomania. So we had the dataset of the patients that can be easily found in the day to day practice of bipolar depression. So this is the primary endpoint of the study and the top line results of this study were announced two months ago, so we can see very robust efficacy of our product with the MADRAS improvement over the placebo between six to eight units.

[01:28:10]

And this is the difference that is statistically significant and clinically meaningful.

[01:28:16]

So when you look at this data, you can see also some trends. So that's good. And we have seen very large effect size between 0.8 1.4, that is increasing with a dose increase. So primary endpoint was met.

And this is impressive in my practice, in my research practice, I have never seen such large effect size in bipolar depression.

[01:28:47]

We have also confirmation of the effect of the drug from secondary endpoints. So as you can see on the slides, we have improvements in both response that is defined as more than 50 percent improvement in MADRS scale. And almost half of our patients remitted at week two. So, again, it's very rarely seen that the remission comes such quickly and in such a large amount of patients. So these secondary endpoints that is also supported by a second depression scale, Hamilton scale, that we use in our study – all of them are supporting our primary endpoint, showing a robust effect of the drug in this study. Just to give an outline of you how we compare to the other products that were approved, on this slide, you can see the placebo-subtracted difference on MADRS. And with that, we can see the response comparison between Falkieri on the left and you can see that the placebo subtracted response on Falkieri to be between 40 to almost 60 percent. And that compares very favorably to approved treatments with quetiapine or olanzapine with fluoxetin to be around 20-25 percent and recently approved agents like lurasidone or cariprazine – you have the responses, placebo-subtracted responses of around 10 to several percent.

Z komentarzem [R15]: Do potwierdzenia – prawdopodobnie zająknięcie i miało być 40 to 60, ale trzeba upewnić się, że faktycznie nie chodziło o 42

Z komentarzem [R16]: Słyszymy „20-few" – prośba o weryfikację

[01:30:36]

And the same is with remission. So here we can see also two-to-threefold higher remission in comparison to approved agents, quetiapine, olanzapine and lurasidone, cariprazine. It's worthy to know that in two agents recently approved, lurasidone and cariprazine, treatment-resistant patients were excluded in phase 3. So it gives even more power to the effect what we can see in our study.

Piotr Wierzbiński: Thank you, Mr. President. It was very exciting. It was a very exciting session and I think that we showed you that psychiatry could be very exciting and I think that esketamine could be a very important drug in psychiatry, because esketamine has very quick action, start of action is very quick because usually we need to wait for the antidepressant drugs. We have changed the paradigm of treatment because, well, usually in our normal practice, we use SSRIs or SNRIs which inhibit the noradrenalin transport to the neuron's serotonin and increase the serotonin and the dopamine in the brain. But now we have esketamine which changes everything because its mechanism of action is quite different.

[01:32:12]

And it's a quick time from the table to the onset or from the respiratory session to the onset.

Z komentarzem [R17]: Prośba o weryfikację 0 czy faktycznie padło słowo onset, czy chodziło o coś innego?

[01:32:21]

So I think that we showed you that psychiatry could be exciting and that maybe we need of course, I'm sure that we need the future researchers about esketamine, because it could resolve the unmet medical need in psychiatry, especially in the treatment-resistant problems with unipolar and bipolar depression. So thank you, Mr. President.

Maciej Wieczorek: Thank you very much.

Piotr Wierzbiński: Thank you, Professor Vieta. Thank you, Professor Soares. It was an excellent session for me and for you also, I think.

[01:32:58]

And our next session is oncology. And oncology is a very important part for Celon Pharma.

[01:33:17]

Welcome. It's me once again, I'm Piotr Wierzbiński, I'm a psychiatrist, I'm a medical doctor and philosophy doctor, and we are in Celon Pharma Headquarters. And with me is Professor Chorostowska-Wynimko, one of the best pulmonologist I have ever met in my life. And still with me is Mr. President, Maciej Wieczorek, CEO of Celon Pharma. And now we talk about oncology, because we know that one of the first innovative programs started within the company was FGFR inhibitor in targeted treatment of cancer.

[01:33:59]

Today, this field is very hot, with many clinical programs running and first agents approved recently. And we have Professor Chorostowska with us because Professor Chorostowska is an ideal person to talk about combining new diagnostic techniques for patient preselections with FGFR receptor treatments. Professor, let me start by asking why FGFR genetic aberrations might be a valid therapy therapeutic strategy?

[01:34:35]

Joanna Chorostowska-Wynimko: Well, indeed, oncology is recently a very rapidly progressing field in medicine and mostly due to the fact that we have understood the importance of targeted treatments in oncology. It's much more effective and allows us really to change the natural history of many cancers. That includes also FGFRs. This is a signaling axis that has been known as crucial for normal development of organs of vasculature and skeletal structure of the body. However, now we understand also that it's important for the development of a number of cancers, and this is due to the fact that this is the signaling that is crucial for cancer cells, development, differentiation, growth and also survival.

[01:35:38]

So all those features that are very strongly linked to cancer, oncology per se; the family of fibroblast growth factor, is a group of our four receptors and as many as 18 ligands.

[01:36:03]

All those receptors are highly conserved trans-membrane kinase receptors that are important in cancer-linked signaling due to the number of aberrations and mostly due to the fact that, as we know now, there could be mutations, there could be translocations and also gene amplifications that result in a gain of function changes and subsequently in cancer development. Those are the so-called driving mutations for many cancers. Among those, cancers with higher incidence of FGFR aberrations are lung cancer, mostly squamous lung cancer, with amplification of receptor one as high as 17 percent.

[01:37:14]

Gastric cancer with the amplification of receptor two are close to 10 percent. And also bladder cancer with a number of mutation in receptor three.

[01:37:27]

Our current experience with targeted therapies in oncology also proves that it's not only important to understand the mechanisms of driver mutation, but also to be able to properly identify selected patients who would respond to the therapy. For that, we need very well chosen biomarkers. Those biomarkers indeed allow us to identify those patients who potentially would respond to the to the treatment. And that could be achieved at different levels, starting from the protein, via RNA, down to our DNA isolated from the tumor cells, but also different techniques could be used.

[01:38:16]

So essentially, in order to have efficient therapy, it's not only important to have the molecule, but also to identify the proper diagnostic method, a method that would allow us to indeed apply the treatment to the most responsive patients. For that, in terms of FGFR axis, different techniques could be used, dependently on the targeted aberration of FGFR. So, as you can see, or we could either use the wide-range scanning NGS, we could target the RNA level as well as protein level or with, for example, immunohistochemistry.

[01:39:16]

Indeed, in our clinical research, we decided to specifically address this question. So not only to develop the molecule, but also to develop the most specific and most effective method of patient selection and therefore the companion diagnostic test development within the trial, very specifically targeting the aberration link to the given cancer. So, for lung cancer, we aimed at looking at the efficacy of FISH, flourescent in situ hybridization, to identify FGFR1 amplification, but also at the protein via immunohistochemistry in gastric cancer.

[01:40:11]

Again, we used FISH and immunohistochemistry techniques to identify aberration in receptor two. And finally in bladder cancer, mutations are the target for the MALDI-TOF mass spectrometry, but also again, protein of immunohistochemistry. Therefore, we hope to achieve the, let's say, ideal set up of identifying the patient with highest efficacy. And this is the fact that has been proven by many clinical trials, the more specific, the more effective diagnostic method, the higher efficacy of the properly chosen molecule.

[01:41:04]

Mr. President, Doctor Maciej Wieczorek still with us. Mr. President, I have a question, I think an important question for our participants. We have a few other FGFR inhibitors in clinical development, what do we know about CPL116 and how this compares to the other inhibitors.

Maciej Wieczorek: Well, actually, FGFR, our CPL110 was not an easy molecule to discover. This is a kinase inhibitor, so with all of kinase inhibitor, we face the problem of selectivity, and this was also the case for our molecule.

[01:41:46]

And on this slide, you can see the pharmacodynamic profile of our molecule. So we have managed to find a molecule that is potent in low nanomolar concentrations. And this potency is quite similar to today in phase 2 AZD4547 from AstraZeneca molecule, so as you can see, we are similarly effective to inhibit the FGFR1, 2 and 3 isoform.

[01:42:19]

When we look at the selectivity, we are a little bit more selective to AstraZeneca compound.

[01:42:26]

And when we look at the other molecules, FGFR inhibitors, we are similarly or more selective, when we compare to others that are now in clinical stage. When we test our molecule, in cell lines, we see consistent inhibition of tumor cells lines that are FGFR-driven and those that lack FGFR genetic aberrations in general, our molecule is inactive. So this profile gave us a rationale to go ahead to move to the animal studies. And we have several lines of confirmation from many animal models using those tumor cell lines, but also patient-derived xenografts.

[01:43:19]

And these models are more informative and translated into the clinical effect that we can have when administering our product to humans.

[01:43:32]

So in all of these models where cell lines or tumors had genetic aberrations of FGFR, we can see very a robust effect in the dose in case of mice between 10 to 40 milligram per kg administered twice weekly. So we have very good preclinical evidence to show effect of our molecule in many tumors.

[01:44:00]

And as you know, we particularly target gastric, squamous lung and bladder cancer.

[01:44:10]

Piotr Wierzbiński: Thank you, Mr. President. To be honest with you, ladies and gentlemen, I thought that psychiatry is fascinating and difficult and quite complicated, but I think I should change my mind because oncology is incredible. And the next question is to Professor Chorostowska. CPL116 is tested in the phase 1.1.b. in solid tumors. And can you please tell us more details about the design of this study and the expected readouts. Is the phase 2 studies design already known?

[01:44:49]

Joanna Chorostowska-Wynimko: So indeed, oncology is fascinating. I very much agree and therefore I am really happy to be part of the joint project developed with Celon Pharma.

[01:45:00]

My institution is part of the ongoing clinical trial, phase 1.1.B and in this trial we are going to enroll patients as per standard three plus three design. The first part of the trial, the initial dose escalation is open to a wide variety of cancers, to patients not only with advanced bladder, gastric and squamous lung cancer, but also with cholangiocarcinoma, sarcoma and endometrial cancer, because in this part, we do not really identify the aberrations.

[01:45:43]

So this status of FGFR is not tested. We started from the low dose of 12.5 milligrams and four cohorts are to be included. However, in the next part, part two and then part three we are going to preselect patients specifically as per biomarkers, as per FGFR aberrations. In part two, this is a dose escalation. Part two, up to four cohorts are to be involved. We intend to identify the maximum tolerated dose specifically and only in patients with squamous lung cancer, bladder cancer and gastric cancer.

[01:46:25]

So as soon as MTD is established, two interim dose cohorts are to be open, also in order to analyze the potential efficacy of our molecule.

[01:46:48]

At the moment, we have already achieved approval from regulators and the bioethics committee. Four centers are actively recruiting, two more are to be started. We already have cohort four active, with 100 mg of the molecule; and cohort five is to be open quite soon. And importantly, in those patients who have already been enrolled into the trial, we observed specific and very positive signals in terms of disease stabilization and, also importantly, no severe adverse effects were observed.

[01:47:41]

I think this is very important for the future trials, hopefully.

[01:47:48]

Piotr Wierzbiński: Thank you, Professor Chorostowska, but we know the head coach is here, and Mr. President, I know that you have additional information about phase 2.

[01:47:58]

Maciej: Wieczorek: Yes. So we are really happy with what we can see in our phase 1.1.B. So the study is running. We expect to have more data in the next months. So we are thinking about phase 2. And given the very fast approval of first FGFR inhibitors in urothelial cancer and cholangiocarcinoma from J&J inside and these approvals were based on relatively small phase 2, 80-90-patient studies. So our phase 2 will consist of two stage parts. It will be a two stage design in which we will recruit in the first stage around 40 patients.

Z komentarzem [R18]: Słowo nieczytelne

[01:48:46]

And in the prespecified interim analysis, we will analyze the futility and response. And depending on the readouts from this interim analysis, we will take a decision to move forward with the study, to recruit around additional 40 patients. So I think this is a very rational design that can be very cost effective, but rationally designed to give up the compound, if not seen effect, sufficient effect after 40 patients. But once the effect is meeting the prespecified criteria, we'' move forward and recruit around 80 patients.

[01:49:36]

So if in these three tumors, gastric, bladder or squamous lung, we can see a similar response, as was seen for the first approved agents like 30 percent more, I think this is a very, very attractive molecule, and then prepare a drug application.

[01:49:53]

So we are very optimistic here. And the phase 2 should start immediately after the readouts from phase 1.1.B, hopefully positive, that can be seen in the next quarters.

Piotr Wierzbiński: Thank you, Mr. President. Thank you, Professor Chorostowska. I agree with you that oncology is very exciting and very complicated. Thank you for your presentation. And I think that for all our participants, it's a huge dose of knowledge because these studies, these potential drugs, and I'm optimistic about the future, about this, we can resolve many problems for many our patients.

[01:50:51]

But the next stage of our meeting today is inflammatory diseases. So stay with us and let us move to the next part of our meeting – inflammatory diseases.

[01:51:11]

With me is Mr. President, Dr. Maciej Wieczorek and Professor Chorostowska-Wynimko, one of the best pulmonologists, as you know that I have ever met in my life. And now we'll talk about inflammatory diseases.

[01:51:26]

We have more and more knowledge about the inflammatory diseases and about pulmonary manifestations, particularly interstitial lung disease in the course of many autoimmune diseases, among them, rheumatoid arthritis. The management of rheumatoid arthritis and interstitial lung disease is a challenge. I know, because many patients who suffer from rheumatoid arthritis are the patients for psychiatry, because they suffer from depression disorder, too, because the pathogenesis of depression and autoimmune diseases is very similar because of immunology. So, Professor, would you share with us this topic?

[01:52:15]

It's epidemiology and current management. Professor Chorostowska.

Joanna Chorostowska- Wynimko: Yes, indeed.

[01:52:21]

The connective tissue diseases are a group, a multitude of diseases with very divergent clinical presentation and importantly involving mostly the respiratory tract. Essentially, in any of those diseases, lungs could be involved. And that very much affects the diagnostics, the follow up and treatment of the patient, but importantly, also the prognostics, the prognosis of the patients.

[01:52:58]

As you can see, the CTD prevalence is not as rare as one might think. Those diseases are actually a very important medical and social problem. And lung involvement is also significant. The higher prevalence of lung involvement is observed in rheumatoid arthritis and in scleroderma.

[01:53:32]

As I said, the clinical manifestations per se might be quite different. Nevertheless, the mortality of those patients is severely affected by lung involvement. Actually, lung involvement is considered as a major risk factor for that in those patients. And I think that very well shows how very important the effective therapeutic approach is to the interstitial lung disease associated with that group of diseases. And I mentioned already rheumatoid arthritis, because this is a quite prevalent disease.

[01:54:21]

It is considered that as many as one percent of population in developed countries is affected by rheumatoid arthritis. And speaking of complication, as many as 40 percent of those patients could actually have some type of lung involvement.

[01:54:45]

As I mentioned, mortality is a significant complication, if I might say so. But please observe that in terms of mortality, actually, the rate in patients with lung involvement increases more than twice in rheumatoid arthritis patients.

[01:55:05]

Lung involvement might have a different histologic and clinical characteristic. Most often, as usual, interstitial pneumonia or non-specific interstitial pneumonia. However, we use quite a similar diagnostic approach, mostly high-resolution computer tomography of the of the chest, as well as pulmonary function tests. There are no, unfortunately, specific biomarkers that could help us to predict the risk of mortality in this group of patients. And also in terms of treatment, we most often use, let's say, an unspecific approach, either using systemic corticosteroids or immunosuppressive agents recently also biologic agents.

[01:56:06]

However, I think from the clinical point of view, it would be really helpful to have agents that would really make our treatment approach more effective.

Piotr Wierzbiński: Thank you, Professor Chorostowska. The immunology system is very complicated. And we are still in Celon Pharma headquarters. Ladies and gentlemen, the next question to Mr. President. We know that CPL116 is the first dual JAK/ROCK inhibitor in the clinical development. As a psychiatrist, I always wondered how such molecules are discovered.

[01:56:42]

And before we move to its clinical potential, Mr. President, can you present the discovery and preclinical efforts with this program?

[01:56:56]

Maciej Wieczorek: Well, actually, JAK/ROCK inhibitor was rationally designed by us.

[01:57:04]

And we have started almost 10 years ago, simply looking for JAK inhibitors at that time. Inhibiting JAK kinases were very, very attractive targets in oncological diseases. We know today there are a few of them approved in many blood tumors. So we did the same. But in the same time, we realized that patients with autoimmune diseases are not dying because of the underlying disease, but are dying because of increased CV risk or because of other manifestations like interstitial lung disease.

[01:57:49]

So we wondered how to modify our molecule to have additional property of having severe risk protection and probably to be effective in fibrosis. And this is the rationale behind looking for those JAK inhibition as antiinflammatory property compound and antifibrotic and CV protection effect that was pursued by us by showing this dual JAK/ROCK inhibition. And we managed that. We found one of the molecules from our very large library to have this dual action. And it's called CPL116.

[01:58:35]

As you can see on this slide, this is a very potent inhibitor with the JAK inhibition on similar potency to tofacitinib, currently the most widely used JAK inhibitor on the market. But we are more preferential for JAK1 and JAK3 over JAK2 kinases. So that's good, because with that, we think we can have a better hematological profile. But in the same time we are very potent on ROCK kinases on both ROCK1 and ROCK2 and here, on this slide, you can see the comparison to Fasudil, the only approved ROCK inhibitor.

[01:59:14]

So we have a very effective, potent and quite selective agent.

[01:59:20]

And on the left you have the selectivity parameters with all of this data we wanted to confirm the anti-inflammatory property.

[01:59:30]

And on this slide, you can see that our inhibitor is a very potent inhibitor of the proinflammatory cytokines. You can see inhibition of interleukin 6 TNF alpha to major cytokines responsible for inflammation in rheumatoid arthritis. But in general, we have the blocking of almost all of proinflammatory cytokines using our inhibitor. But also, we can see effects in both in vitro and in animal studies effect suggesting that we are very strong, very potent inhibitor of ROCK kinases.

Z komentarzem [R19]: A może in fact?

[02:00:14]

And here on this slide, we can see that we are blocking downstream proteins in ROCK signaling. This is phosphorylation of MLC and MYPT1. And this data are also confirmed in very elegant, biographic experiments. So again, we can see the vasorelaxant effect and anti-contractile effect, suggesting ROCK inhibition with our agent.

[02:00:43]

So with all of these preclinical data, we went to animals and we have very robust efficacy data in almost all animal models where we are using anti-inflammatory JAK inhibition with RA, psoriasis, lupus, Crohn's disease. But we have unexpectedly, we can see effect in those models, animal models, that require both anti-inflammatory and anti-fibrotic effect. And this is pulmonary arterial hypertension, where we compare our molecule to Sildenafil today, one of the most commonly used agent in pulmonary arterial hypertension, but also in idiopathic pulmonary fibrosis we use nintedanib as our active control.

[02:01:31]

And again, we have a much more consistent effect of our molecule in comparison to nintedanib, again, today, the standard of care in idiopathic pulmonary fibrosis. So, these data really are very optimistic. And I think we have very, very strong evidence to have those anti-inflammatory and anti-fibrotic activity with our agents. On this slide, you can see a comparison in RA study in collagen-induced RA model with tofacitinib, JAK inhibitor and a similar nominator doses.

[02:02:14]

We have a more pronounced effect with our agent in comparison to tofacitinib. So we were a little bit afraid of toxicity, given this dual mechanism of action. So we are really surprised, positively surprised, that we're not very toxic in the GMP toxicology program. So when we compare our agents to approved JAK inhibitors, we can see, based on no observed adverse event level, an order of magnitude higher levels for

our compounds in both rodent and non-rodent studies in comparison to baricitinib, tofacitinib and upadacitinib – JAK inhibitors that are approved.

[02:03:01]

So this is really good data. And when we sum up the Jack Rock inhibitor, I think we can expect cardio protective potential with this ROCK inhibition.

[02:03:19]

There are more and more data suggesting that statins and many inhibitors that are inhibiting ROCKs, some of the cardioprotection potential comes from ROCK inhibition. We have fasudil approved in some kind of stroke and we can have additional anti-inflammatory actions through ROCK inhibition. This is mostly in interleukin 17 axis. So with all of that, we can explore new avenues of testing this agent in such settings like idiopathic pulmonary fibrosis or interstitial lung disease associated with many autoimmune diseases, and particularly rheumatoid arthritis.

[02:04:09]

Joanna Chorostowska-Wynimko: And indeed, pulmonary arterial hypertension that you have mentioned is a strong risk factor for mortality in those patients, in patients with connective tissue disease, interstitial lung disease, and therefore, this is a complication that we fear very much as a clinician. I do believe that this signal, it's still a signal, as the data come from the preclinical phase, however, I, as a clinician, consider as a very optimistic

Piotr Wierzbiński: Very important information, I think for us.

[02:04:43]

But the next question to ask is: I've been told that CPR 116 was granted expedite regulatory path due to Covid-19; potentially. What was the rationale behind that?

[02:05:00]

Well, indeed, Covid-19 is a hot, is a burning topic at the moment and definitely at the highest unmet need we could actually discuss today.

[02:05:14]

And as you know, in, on average 20 percent of patients, the Covid-19 is complicated by the bilateral pneumonia. And those patients are most often admitted to the hospital. They need the hospital care and, in many of them, the massive immune response develops so-called cytokine storm. Those patients,

unfortunately, develop lung tissue damage, respiratory failure and need support in terms of either oxygen therapy or mechanical invasive, non-invasive ventilation.

[02:05:56]

So up to date, we have essentially three clinical trials proving the effectiveness of either antiviral therapy, and this is remdesivir, as you know, or anti anti-inflammatory treatment or with dexamethasone. But those two clinical trials proved that with those treatments, we actually targeted two different groups of Covid-19 patients with acute clinical presentation as per the ordinal scale of Covid-19 severity. Remdesivir is most potent in group 4; those are patients that do not as yet need supplemental oxygen treatment. And whereas the dexamethasone, so anti-inflammatory treatment, is most effective in group 7.

[02:06:56]

So those patients who are admitted to and treated due to very severe presentation and are treated with mechanical ventilation. So that leaves us with the so-called grey zone of group 5 and 6 as shown on this figure. And very recently, the New England Journal of Medicine published the results from the clinical trial or with JAK1, JAK2 inhibitor, very promising results that showed that the combined treatment of barcitinib and remdesivir versus placebo plus remdesivir proved very effective in patients needing oxygen supplementation or noninvasive mechanical ventilation in terms of time to recovery, in particular group 6, so those are patients treated with NIV.

Z komentarzem [R20]: Czy chodziło o NIV (non-invasive ventilation)?

[02:08:01]

In those patients, time to recovery was on average 10 days, whereas in the group treated with remdesivir, only 18 days; I think that shows that quite a spectacular result. And therefore, we could really pose a question whether treatment with the dual JAK/ROCK and anti-inflammatory and anti-fibrotic inhibitor might be hypothetically the treatment for Covid-19 severe patients.

[02:08:42]

Piotr Wierzbiński: Wow.

[02:08:42]

I have no anxiety now, because JAK/ROCK inhibitors can improve the natural history of Covid-19, probably.

Joanna Chorostowska-Wynimko: Might improve, this is the, I would say, hypothesis, but I think very fascinating and quite exciting hypothesis that I would like really to research.

[02:09:08]

Piotr Wierzbiński: But the future sounds optimistic, I think.

Joanna Chorostowska-Wynimko: Well, yes, I think the more we know, the higher the probability that we will find a solution for the burning question and the highly unmet need, Covid-19.

[02:09:23]

Piotr Wierzbiński: But when we talk about the future, Mr President, you have started phase 1 clinical development. Where are you with this study and what is planned next?

[02:09:35]

Maciej Wieczorek: Yes. So we are in very good momentum today because we are just finishing phase 1. The study has started last year in the first quarter, and we have already completed single dose ascending, food cohort interaction study. And today we will administer some patients with multiple ascending doses to see what is the PK safety and different doses of this compound. Up to now, the safety results are very good. We don't see any toxicity from the administration of the compound.

[02:10:15]

The initial PK profile is also very, very good. So we look forward to the phase 2 program.

[02:10:22]

And as there are plenty of clinical settings in autoimmune diseases, we want to initiate a few proof of concept studies targeting both RA, psoriasis, but also RA interstitial lung disease and idiopathic pulmonary fibrosis, and we want to be smart in the design of the studies.

[02:10:44]

Mostly, the studies will be driven by biomarkers as quickly as possible to have readouts and covid today is a great setting.

[02:10:55]

We know that hundreds of thousands of patients in the hospital, so potentially we could, starting from September, start phase 2/3 study with our agent in probably the patients in stage five and six, as Professor Chorostowska mentioned, with a more predictable benefit in this patient population. So if we think about composite endpoints with the progression, mortality and probably lung impairment of the disease, we could have with 500-600 patient study statistical power to see clinical benefits with our agent.

[02:11:45]

So, very, very attractive times, very attractive momentum for this compound and we are very optimistic for the future.

Piotr Wierzbiński: Thank you, Mr. President. So, as you see, the future sounds optimistic because Celon Pharma's focus is on many molecules and we need immediately next phases, Mr. President, I think so. And so, I would like to thank all the experts in this excellent key opinion leader session. Thank you, Professor Chorostowska once again for being here in Celon Pharma headquarters.

[02:12:27]

Thank you, Mr. President. And thank you, Professor Eduard Vieta from Barcelona. And thank you, Professor Soares from Houston. I think, I hope that you learned a lot of hot therapeutic areas and huge unmet needs in these therapeutic areas. Now, let's go back to Małgosia.

[02:12:52]

Małgorzata Siewierska: Thank you for this interesting session; as you have noticed, as a company, we prefer to focus on drug development, not creating television productions, so please forgive us for minor imperfections that have occurred during the recording. Well, connecting two continents at the same time can be challenging. But now we move to the Q&A session. To participate in it, please click the Teams link available on our website. Just right now, we kindly ask you to provide your full name and surname when joining the session.

[02:13:32]

We want to meet you as well. And please ask the questions in English.

[02:13:42]

The participants of this session will be company representatives as well as experts from the KOL session, Professor Chorostowska-Wynimko. And we have together with us Professor Soares, straight from Texas. So please join the teams link available on the website just right now. Take your time and we'll get back to you in a moment.

[02:17:21]

So let's start our Q&A session. Thank you for all the questions that we have already received. It seems that we raised interesting points, in all presentations. So let's try to take a closer look at them. Feel free to ask your question via the chat available on our website, via the TEAMS chat. But if you prefer to speak in person to our guest, there is also such a possibility for you. Just use the "raise hand button" in Teams to do it and we'll give you the floor.

[02:17:58]

So I would like to address the first question to Professor Chorostowska. Do you agree with the statement that the medicine in the post-covid area, especially in the area of lung diseases, will take on a new dimension? And what medical challenges in this area will we be facing soon? And this is a request for your opinion on this topic.

Joanna Chorostowska-Wynimko: Well, definitely, as we mentioned, Covid-19 is a highly unmet, or, as it was said, a burning need at the moment, mostly due to the acute Covid-19 presentation.

[02:18:41]

This is the wave, or the problem, we are currently facing in our hospitals, but also in the outpatient clinics. And I think the potential and the need for new therapies has been very well presented. Nevertheless, as you correctly posed the question, there is so much more about the current situation than only the acute phase of Covid-19, and I really do see it in my everyday practice, clinical practice. By that I mean the post-covid patients, both the so-called long covid patients or patients that have actually gone through the acute phase and still do present with the respiratory symptoms.

[02:19:38]

But also and even those patients who might have not been actually very severely ill due to Covid-19, however, start to develop or to present symptoms. So all those groups of patients would definitely need specialized respiratory care. And I do believe that for those patients, we probably would also need to develop a very specific and very well-tailored follow up programs that would include the clinical follow up, but also the new and dedicated treatment approach.

[02:20:17]

And here I would like just to mention the new option for JAK/ROCK inhibition, still, this is a working hypothesis, this is a certain potential I see. We discussed the acute phase, but if you think about the patients with long covid or continuous respiratory presentation of Covid-19, I could really think about the potential clinical application, again, hypothetic, for the anti-inflammatory and anti-fibrotic activity or treatment. And so in that aspect, I think the definitely there is much to be done in this field.

[02:21:04]

Małgorzata Siewierska: Thank you very much. Coming back for a little while to bipolar disorders and I have a question addressed to Professor Soares.

[02:21:15]

When talking about the unmet need for bipolar depression, what features of any new potential treatments for this condition would you consider to be the most desired by clinicians?

[02:21:30]

Jair Soares: Well, that's an area of real need. There are few medications available currently and efficacy for them isn't that great. They also take a while to work and have a higher risk of actually making the patients switch into a manic phase. So a new medication for bipolar depression that would work reasonably fast, that would be well tolerated and carry lower potential to switch for mania or hypomania would be really well received because that's an area of real need for our patients.

[02:22:16]

Małgorzata Siewierska: Thank you, Professor Soares. And actually, we have a first question for from our audience. Ms. Katarzyna Kosiorek, the floor is yours.

[02:22:26]

Please unmute your mic, so we can hear you properly. Take your time, we're waiting for your questions, but you are still on mute. OK, it seems like we are facing some technical issues, external ones, so we have another external question. Please [...], the floor is yours. We are looking forward to your questions.

[02:23:24]

X: Hi, can you hear me OK?
Małgorzata Siewierska: Yes, we can hear you good.
X: OK, great. This is [...] from [...]. Thanks for the presentation, it was really great. Three questions. So NICE rejected Spravato last year and I just wanted to know your thoughts and implications for your product in going forward. Then the second one was on the tofacitinib JACK/ROCK [...]

Z komentarzem [R21]: Nie usłyszeliśmy nazwiska

Z komentarzem [R22]: j.w.

Z komentarzem [R23]: Niestety, nieczytelne

[02:24:02]

Do you do you see this safety issue being a whole class issue and with competition emerging from tech to how do you see the landscape emerging? Right. And then finally, which companies, in your view, could be the natural partner for the neuroscience portfolio? Thank you.

Maciej Wieczorek: Thank you very much. These are excellent questions and maybe let's start with this first question about Spravato refusal in NICE.

[02:24:38]

So, you know, this has economics decisions. We always look at the magnitude of effects and the costs of the treatment. So in Spravato in unipolar depression, the magnitude effect was not as large in phase 3

and at the same time Spravato, the monthly therapy, costs around three to five thousand dollars. So I think this was taken into account by British, health care payers, once assessment of the application.

[02:25:18]

So it's difficult to say whether the same can be used when evaluating our application. We are targeting different diseases, treatment-resistant bipolar depression with much less therapeutic options. And of course, let's see what will be the magnitude of benefits of our therapy in different indications.

[02:25:44]

So I would not be very afraid and scared with what's happened with Spravato in the British assessment. We know British regulators, assessors are very tough and they use that strategy for negotiating better prices for the future. Moving to your second question. This is about tofacitinib safety and whether this is the class effect or not, we don't know.

[02:26:17]

When we have data from other agents, I think data sets for upadacitinib are not suggesting any massive risk, cardiovascular risk for these agents, but when we look from the perspective into the whole class, we can see that they are associated with some, you know, worsening of lipid profile. All of them are associated with increases in total cholesterol and LDL in the same time as some increases in HDL is seen. So I think this is common for all of these agents. So they impair lipid profile. But at the same time, we can see different, you know, impact of these agents, different JAK inhibitors on platelets.

[02:27:15]

Some of them increase platelets, some of them decrease platelets into different hematological properties. So the answer is, we don't know. We know about tofacitinib, that it's associated with some increase in CV risk. Whether this will be a class effect, we don't know. My personal feeling is that we cannot see as much for other agents as we can see for tofacitinib. But again, we should not be compared to JAK inhibiters because we have ROCK inhibition, vasorelaxant, anticontractile. We know it's good for our body to have ROCK inhibition and statins do that, particularly newer statins, rosuvastatin, atorvastatin and, less so, simvastatin.

[02:28:02]

So those statins that we know are associated with decreased CV risk in large studies. So, I think we are optimistic that this is not class effect and we think our agent has clear differentiation here. And your third question was...

Jacek Glinka: I can handle that.

Maciej Wieczorek: You can handle, please.

Jacek Glinka: So we are testing the waters here in a way that Falkieri is our first program, which is now being moved to the phase 3 clinicals.

[02:28:50]

In a way, it's ready for partnering. We are therefore evaluating different strategic options. One of them is to look for the global partner, that is strong, in CNS. So, you know, all these big names here, or alternatively, to look for a partner on a regional basis to divide the rights into US, Europe, China and Southeast Asia, the rest of the world, and to try to partner with different partners in these territories.

[02:29:22]

These partners could, of course, include also the global names that we would look to discuss, the first option. The third one, though, that we are also evaluating is to move to the phase three clinicals without the partner and then subsequently reevaluate the options when we will be more advanced with phase three clinicals. So we are, in a way, evaluating all such options right now and probably need at least a few more weeks, if not months, for us to finally decide which way we would go.

[02:30:02]

X: That's really helpful. Thank you.
Małgorzata Siewierska: Thank you. Do you have any follow up questions to this part? OK, if not, we're moving back to Texas again. Professor Soares, another question to you. Can you give us your thoughts on the use of ketamine in mood disorders in the past and provide some comments on various forms of esketamine administration that are available right now?

[02:30:39]

Jair Soares: Right. So ketamine has proven to be a very important advance in treating depression in patients with mood disorders. I would say it's probably the biggest advance in treating mood disorders patients for the past decade or so. And the reason is that it seems to work really fast. And I mean, where you see differentiation, I mean often like after a week. Also, the efficacy is good, obviously. It started with the intravenous administrations. That's a generic drug where there was not much there for any company to try to pursue that, as you know, a potentially approved FDA product.

[02:31:37]

However, there is a lot of off label use of injected ketamine for treatment-resistant patients with depression. So it's used on an off label basis quite a bit actually. It changed a little bit with the advent of esketamine, which is, what is available in the US, is really being hailed, is provided for and it's easier to

administer, the effect seems to be reasonably fast. So that has been an important improvement in the toolbox we have to treat patients with unipolar depression.

[02:32:18]

That's what the approval is. And obviously these things need to be tested specifically for bipolar depression. Bipolar depression is an even bigger unmet need because those are generally difficult to treat patients and the available medications aren't really as efficacious. So there is a need for a product tested specifically for bipolar depression, primarily if they work fast. Tolerability is good and I think efficacy is good as well for treatment-resistant patients. So I'm very enthusiastic about the possibility to see new data, phase 3 trials, that would address that unmet need with new products that would have the potential for fast effects and good tolerability, and also easy to administer better than the injections of ketamine. There have been small studies trying to administer ketamine in other ways, like subcutaneous administration, oral administration, with some interesting results early on with just regular ketamine. But again, these [...] there's just not enough interest there from [...].

Z komentarzem [R24]: Fragment nieczytelny

Z komentarzem [R25]: Połączenie przerwane

Małgorzata Siewierska: I encourage you to use raise a hand button in Teams to ask your questions in person to our guests, and I can see and hear that we have Kasia Kosiorek with us.

[02:34:00]

Please ask your questions to the participants.

[02:34:06]

Katarzyna Kosiorek: Good afternoon, everyone. Can you hear me?

Małgorzata Siewierska: We can hear you properly, the floor is yours.

Katarzyna Kosiorek: Sorry for the inconvenience. I have several questions. First, I would like to congratulate on the Falkieri phase 2 results in treatment of resistant bipolar depression and in terms of observed therapeutic size, as you mentioned, how is this compared to the effect size of other agents that are used in the indication of BPD, such as atypical antipsychotics or mood stabilization drugs?

[02:34:42]

And next part of the question, the readouts from the Falkieri phase 2 have indicated a high significance, clinical significance in the treatment of BPD and how can these results help you in terms of discussion with regulators. Do you see the potential for the expedited designations, as a breakthrough therapy designation, for example? Thank you.

Maciej Wieczorek: So maybe the first question, Professor Soares, would you like to address the first question about effect size that we have, your thoughts about that?

[02:35:19]

Jair Soares: Yeah, sure. You know, the data that I've seen from phase 2 trials looks very robust. The effect size is impressive compared to the other few available treatments in this area of bipolar depression. So it looks very promising. Obviously needs to be replicated and expanded in a phase 3 study but looks very promising.

Maciej Wieczorek: Yes, so we have a particular focus on that, and I remember when we look at the data and extract effect sizes for antipsychotics, we can see effect size of between 0.3 to 0.6, 0.7 maximum.

[02:36:06]

So this is like small to medium effect size. So our effect size is you know, we are doubling the effect size in our study. So, I have not seen the effect size of our magnitude in any previous studies. As relates to your second question in the expedited path, well, as I said, we are working together with Parexel.

[02:36:37]

This is our CRO that is supporting us in preparation for EMA and FDA.

[02:36:45]

And I can just say today, yes, we are evaluating the possibility for breakthrough designation for bipolar depression and we have not yet filed such an application, but I can say that this is very likely that we have sufficient data to ask for that.

Katarzyna Kosiorek: OK, thank you. So if I have a chance, I would like to ask another question, and this question is related to the FGFR inhibitor. In terms of this project, recently, the company Five Prime Therapeutics has shown. So to do this, they project to be quite effective in the gastric cancer therapeutic area.

[02:37:37]

Do those results change anything in terms of your selected therapeutic areas, gastric cancer in particular.

Maciej Wieczorek: Thank you. Professor, would you like to commence on gastric cancer?

[02:37:53]

What's your thinking today?

[02:37:56]

Joanna Chorostowska-Wynimko: Well, I am a respiratory specialist, so I don't really feel an expert in the field of gastric cancer. Nevertheless, well, with personalized medicine, I think the major issue is, as we discussed, not only to have the active and potent molecule, but also to identify the right cohort or the right group of patients before. With FGFR inhibitors, if you look at this group of molecules, per se, the major problem have been actually, first, the activity of the molecules, the inhibitory activity of the molecules, so the treatment or pharmacological potential that is interesting from the point of view of drug development.

[02:38:42]

But the second problem, and, actually, in my opinion this is equally important, as shown by a number of clinical trials, is the really specific and up to the point identification of patients. I mentioned in my presentation that the clinical trial was designed alongside with discovery or proof-of-concept of dedicated companion diagnostic. And I think this is as important as really providing the optimal characteristic of pharmacokinetics and pharmacodynamics of the drug.

[02:39:35]

And that actually, in my opinion, was a major obstacle and a major problem in published clinical trials. But that very specific identification of, let's say, responders, the patient who potentially would respond to the treatment.

[02:39:54]

Maciej Wieczorek: I would like to add that this specific study that was published with monoclonal antibody targeting FGFR from Five Prime, for us, it was really something new because they have found that the overexpression of FGFR2 is not in 10 percent of patients that we thought. And our results from our own studies from Poland suggested the same, but it's closer to 30, even more percent of patients.

[02:40:27]

So, one reason is that the Ruanda's study in also Asian countries, and probably we have much more prevalence of these FGFR overexpression in Asia. But that's good. I mean, it means that if we think about gastric cancer and we have much expression, it's not in 10 but 30 percent of the global patients for sure, it's more attractive for this product. And we look forward to testing our agent in gastric cancer. And maybe it's a little bit, you know, in front of, you know, attractiveness of this treatment.

Z komentarzem [R26]: Prośba o weryfikację

[02:41:15]

Małgorzata Siewierska: OK, thank you very much. Do you have any follow up questions to this part?

Katarzyna Kosiorek: Yes, yes, thank you. The last question is related to the JAK/ROCK inhibitor. And with regard to this project, it is known that antiinflammatory therapy with similar agents such as tofacitinib, carries some cardiovascular risk, as you mentioned, and the therapy with ROCK inhibitors significantly reduce the number of cardiovascular events. So could you tell us something more about the clinical benefits of that dual mechanism of action of your project, especially in the context of cardiovascular benefits and, for example, other tissue protection such as lung and renal protection? Thank you.

[02:42:05]

Maciej Wieczorek: I think this is a very large topic and we don't have time to discuss all of that. But of course, it's too early to say that we have clinical evidence of this CV protection.

[02:42:18]

We think there are very good chances to see that clinically, based on preclinical experiments, based on the mechanism of action and based on target inhibition, we can see from phase 1.

[02:42:33]

So with our PK PD simulation, we have good data to think that we could target those JAKs and ROCKs with our agent in the therapeutic doses. But, of course, we need to design our phase 2 and phase 3 program, first using biomarkers in phase 2, and then clinical endpoints in phase 3, to prove that. So it's too early to say that we will deliver that, but we are well positioned and the agent is ideal to see the effect.

[02:43:12]

It goes beyond simple JAK inhibition and I think this is the first very attractive agent that we should test this CV protection, CV risk protection with that in the autoimmune diseases that are, as I said, we have a real CV risk in these settings, in these diseases.

Małgorzata Siewierska: Thank you. Thank you for your questions and for the answer. This is, ladies and gentlemen, the last chance to use the raise hand button.

[02:43:46]

But now we will move into the questions that we have already received via email during the session. And I would like this one to address to Jacek Glinka, because as far as I know, he will be very happy to answer it. Well, Salmex continues to be the growth engine of your generic business. Given your ambitious plans to further grow your export sales, will you have to expand your manufacturing capacity in case you get approvals to launch this product in China or in the U.S.?

[02:44:18]

Jacek Glinka: That's a tough question, I would say. Maybe. Right now, our current capacities are at the level of eight million inhalers per year. We are increasing that this year to 11 million inhalers. I think that last year, our total production was at the level of 1.3, 1.4 million inhalers, which means that we could talk about like an order of magnitude bigger capacities than we have current demand. Obviously, China and the US are big markets and therefore, once we enter these markets that the capacity might not be sufficient.

[02:44:58]

We are planning to enter the Chinese market more or less two, three years from now. We are finishing the studies and subsequently we would file for the registration. So probably we could talk about this timeframe when we would launch in China and subsequently probably slightly later in the US. We would have enough time to see if there is a need to further increase the capacities. We have done that last year, quadrupling the level of capacity so we can do it again if need be.

[02:45:35]

But for the time being, we are, I would say, fully secured with the capacities for all the markets, maybe even including China and the US.

Małgorzata Siewierska: Thank you. And another one, this one is probably addressed to Professor Chorostowska. What percentage of diagnosed patients are currently being tested to determine the FGFR mutations? And how do you expect it to ramp up with the following launch of these two new agents for bladder cancer and other cancers?

Joanna Chorostowska-Wynimko: Thank you very much.

[02:46:12]

Well, actually the answer depends very much of the local or the national policy and the regulators.

[02:46:22]

And as an example, I could refer to two opposite, let's say, clinical scenarios. One would be United States. If one looks at the current guidelines, then definitely wide genomic profiling is the preferred option, for example, in lung cancer. This is actually the recommended trigger diagnostic strategy to profile your patient very early prior to the first line, prior to any therapeutic decision. We know very well it has been proven by a number of clinical trials, as well as clinical practice, that the patients with a driver mutation should optimally be treated with the personalized approach right away, by which I mean starting from the first line.

[02:47:18]

So [...] with Y genomic profiling, FGFR aberrations would be actually identified.

Z komentarzem [R27]: Fragment nieczytelny

[02:47:29]

And the opposite scenario is Poland. I think this is also a very good example of the clinical practice that is very much tailored by the local reimbursement policy or the availability of specific treatments.

[02:47:53]

So FGFR inhibitors are not reimbursed in Poland by health insurance, public health insurance. Therefore, it's not a routine part of diagnostics. It's not a routine part of testing. However, we do it, we look at those aberrations as well, providing the patients with profiled broadly with new generation sequencing and then those patients might receive treatment only within the clinical trial setting.

[02:48:24]

Therefore, you could see the different diagnostic strategies that heavily depend on the actual treatment options, treatment possibilities. And that also would very much reflect on the numbers you ask about. I cannot really say in Poland that would probably be a very small number of patients. However, I expect that in the United States it really very much depends on when and where the patient is being diagnosed in the bigger, leading oncology centers.

[02:49:09]

Definitely the majority of patients are widely profiled and therefore are also potential candidates for that group of drugs. Thank you.

Małgorzata Siewierska: Thank you, thank you very much for your answer. We have another question, which was addressed on chat some time ago from Robin Jan. Does it make sense for a company of that size to concentrate on such different areas instead of stick with one or two?

Z komentarzem [R28]: Prośba o weryfikację

Maciej Wieczorek: So this is a very good question, and I think this question I tried to address in the first part of the presentation, so it's not typical for such size of company in the US to have such a broad pipeline of innovative drugs.

[02:50:05]

But we must remember that we are unique in the sense that we have organically grew in the last two decades and we implemented strategies to have a broad pipeline. And we also have a very unique financing model. And within this model, we have many sources of financing, so we went broad in our product development and I think it has lots of advantages because we are securing risk of failures that are inevitably, you know, linked to this type of business.

[02:50:50]

So I think we have the best strategy today, in the country where we are and with the story we have. So this is the response. I think this is the optimal strategy for us. We go broad, but we are securing in both financial and attrition.

Jacek Glinka: I could add to that, if you allow, Maciej, that, you see, we have 20 years of experience in development, initially generics, then innovative products. With that we have built the organization, which is today 500 people, of which almost 200 are scientists, which have gained the relevant experience over the course of years in this therapeutic categories that we focus on.

[02:51:48]

So yes, there is four, not one, but within these four areas, we believe we build sufficient content, robustness and expertise that is supporting us. And we could say that we can build an effective way to manage these programs and move them as we do without many substantial failures from preclinical to phase 1, phase 2 and subsequently phase 3 and commercialization. We believe we can do that. We have a strong and robust organization with a lot of expertise.

[02:52:20]

Moreover, we are leveraging our network of outside third party experts being CRO, CMO, CDMO, whatsoever. So we have built that expertise over the 25 years of working on this market. And I think that that is also part of our unique DNA and our unique position in the biotech sphere.

Małgorzata Siewierska: Thank you. Thank you very much. Actually, I cannot see any new questions. So that's maybe the time to come to some conclusions.

[02:53:00]

But before that, thank you, thank you very much for your participation in your part. Thank you, our guests, for all the answers if and any other will come up in the nearest future, feel free to ask them via email directly to the Investor Relations Department. The presentation after today's meeting together with Webcast will be today available also in our website. So please, you can go back to it whenever you want. And now I would like to invite Maciej Wieczorek to sum up today's meeting. Thank you.

[02:53:38]

Maciej Wieczorek: Again, thank you very much for participating in this first Capital Markets Day of Celon Pharma. And I hope you got an update of our current operations, our ambitious pipeline of new products. We are a very ambitious company, hungry for success, and we hope in the next quarters we will deliver what we said today. So thank you very much and we hope to see you in the next meetings.