SUPPLEMENTARY MATERIAL

Title: Single-tablet combination therapy of macitentan/tadalafil for patients with pulmonary arterial hypertension: qualitative interview study of the A DUE phase 3 trial

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Supplementary Table S1: Patient discussion guide outline.

Patient Discussion Guide Outline	
Discussion Guide Section	**Objectives and sample questions**
Disclosure and Background Information	• To facilitate rapport building between interviewer and the participant. • To introduce the structure of the interview, cover disclosures, and reconfirm consent to record the interview.
Previous Experience with Treating PAH	• To understand how the participant felt about the number of tablets/pills they took for PAH (and other comorbidities) just before the trial started. o Could you tell me if the number of tablets/pills for PAH (and other conditions) you took per day affected your day-to-day life? o Did you ever forget to take your tablets/pills for your PAH?
Treatment Experience During the Clinical Study: Double Blind Portion of the Study	• Understand the patient experience of taking the PAH medication in the double-blind period of the study - 4 pills. o During the double-blind period, how easy or difficult was it to stick to the instructions of taking the 4 tablets/pills at the same time each morning? Why is that?
Treatment Experience During the Clinical Study Open Label Portion of the Study	• To understand the patient experience of taking a single tablet in the open-label period of the study. o Could you talk to me about what it is like to receive the current PAH treatment (1 tablet/pill)?
Patient Adherence to the Treatment	• Understand the patient's experience of adhering to clinical study treatment. o Could you tell me if taking fewer tablets/pills is meaningful or important to you? Why is that?
Ideal PAH Treatment	• Understand from patient perspective the ideal PAH treatment. o What would the ideal PAH treatment look like for you?
Wrap-up	• To gather any additional insights and thank the participants.

PAH, pulmonary arterial hypertension.

Supplementary Table S2: Clinician discussion guide outline.

Clinician Discussion Guide Outline	
Discussion Guide Section	**Objectives and sample questions**
Disclosure and Background Information	• To facilitate rapport building between interviewer and the participant. • To introduce the structure of the interview, cover disclosures, and reconfirm consent to record the interview.
Approach to Treating patients with PAH	• To understand the clinician treatment approach typically used for patients with PAH. o Are you aware of the latest ESC treatment guidelines for patients with PAHs?
FDC Therapy and Patient Ease of Use During the Clinical Trial (both periods)	• To understand experience of administering the macitentan and tadalafil (M/T) FDC treatment to patients during the open-label period of the study. o Do you think taking the single FDC tablet during the open label portion of the study (1 tablet) was easier or harder when compared to taking multiple tablets during the double-blind period (4 tablets)? Why was that?
Suitability and Impact of the M/T FDC Tablet	• To understand from their perspective the suitability and impact of a single M/T FDC tablet for the wider population of patients with PAH. o What do you think about the suitability of the single M/T FDC tablet for the wider population of patients with PAH, if approved?
Wrap-up	• To gather any additional insights and thank the participants.

ESC, European Society of Cardiology; FDC, fixed dose combination; M/T, macitentan and tadalafil; PAH, pulmonary arterial hypertension.

Supplementary Table S3. Date and details of IRB/EC approvals at all participating sites.

Site	Country	Patient interviews conducted	IRB/EC name and address	Date of approval
BR10001	Brazil	No	Comitê de Ética em Pesquisa da UFMG Comitê De Ética em Pesquisa da UFMG, Av Presidente Antonio Carlos 6627, Prédio Da Reitoria – Sala 7018, Belo Horizonte, MG, 31270-901, Brazil	Jun 22, 2020
BR10002		Yes	Comite de Etica em Pesquisa da UNIFESP/EPM Comite de Etica em Pesquisa da UNIFESP/EPM, Rua Francisco de Castro No.55, São Paulo, SP, 04020-050 Brazil	Jul 20, 2020
BR10003		No	Comite de Etica em Pesquisa da PUCRS Comite de Etica em Pesquisa da PUCRS, Avenida Ipiranga, 6690, Prédio 50, sala 703, 3º andar, Porto Alegre, RS, 90610-000, Brazil	Sep 18, 2020
BR10004		Yes	Comitê de Ética em Pesquisa do hospital Madre Teresa Comitê de Ética em Pesquisa do hospital Madre Teresa, Av. Raja Gabáglia, 1002, Gutierrez, Belo Horizonte, MG, 30441-070, Brazil	Jul 31, 2020
BR10008		No	Comite De Etica Em Pesquisa Da Universidade Federal De Goias Coep/Ufg Comite De Etica Em Pesquisa Da Universidade Federal De Goias Coep/Ufg, Primeira Avenida, S/N, Setor Universitario, Goiania, GO, 74605-050, Brazil	Apr 17, 2020
BR10010		Yes	Comissão de Ética para Análise de Projetos de Pesquisa do HCFMUSP Comissão de Ética para Análise de Projetos de Pesquisa do HCFMUSP, Rua Ovídio Pires de Campos, 255 - Sala 505, Prédio da Administração, São Paulo, SP, Brazil	May 08, 2020
BR10014		No	Comitê de Ética em Pesquisa da Faculdade de Medicina de Botucatu Comitê de Ética em Pesquisa da Faculdade de Medicina de Botucatu, Chacára Butignoli s/n, Rubião Júnior, Botucatu, SP, 18618-970, Brazil	Sep 10, 2021
DE10006	Germany	Yes	Ethikkommission der Universitätsmedizin Greifswald; Institut für Pharmakologie Ethikkommission der Universitätsmedizin Greifswald; Institut für Pharmakologie, Felix-Hausdorff-Str. 3, Ethikkommission der Universitätsmedizin Greifswald, Institut f. Pharmakologie, Greifswald, 17487 Germany	Oct 10, 2019
ES10013	Spain	Yes	CEIC Hospital Universitari Vall d Hebron CEIC Hospital Universitari Vall d'Hebron, Paseo Vall d'Hebron, 119-129, Institut de Recerca Hospital Universitarivall d'Hebron, Barcelona, 08035, Spain	Aug 13, 2019
MX10001	Mexico	Yes	Comité de Ética en Investigación del Instituto Nacional de Cardiología "Ignacio Chávez" Comité de Ética en Investigación del Instituto Nacional de Cardiología "Ignacio Chávez", Juan Badiano #1, Colonia Sección XVI, Delegación Tlalpan, Mexico City, Mexico City, 14080, Mexico	Jul 24, 2019
PL10001	Poland	No	Komisja Bioetyczna Centrum Medyczne Ksztalcenia Podyplomowego Komisja Bioetyczna Centrum Medyczne Ksztalcenia Podyplomowego, Marymoncka 99/103, Warszawa, 01-813, Poland	Jul 11, 2019
PL10002		No		
PL10004		No		
PL10005		Yes		
PL10007		No		

TR10003	Turkey	Yes	Marmara University Medical of Faculty Clinical Research Ethics Committee Marmara University Medical of Faculty Clinical Research Ethics Committee, Başıbüyük Mah. Maltepe Başıbüyük Yolu Sok. No: 9/2, Istanbul, Maltepe, 34854, Turkey	Feb 07, 2020
TR10009		No		Jul 26, 2019
TR10010		No		
TR10012		No		
TR10014		Yes		Mar 06, 2020
TW10001	Taiwan, Province Of China	Yes	National Taiwan University Hospital, Research Ethics Committee D National Taiwan University Hospital, Research Ethics Committee D, No. 7, Chung-Shan S. Rd. Zhongzheng Dist., Taipei, 10002, Taiwan, Province of China	Aug 26, 2019
TW10002		Yes	Institutional Review Board, Taipei Veterans General; Hospital Institutional Review Board, Taipei Veterans General Hospital, No.201, Sec. 2, Shipai Rd., Beitou District, Taipei, 11217, Taiwan, Province of China	Sep 11, 2019
TW10004		No	Kaohsiung Veterans General Hospital Institutional Review Board Kaohsiung Veterans General Hospital Institutional Review Board, No.386, Ta-Chung 1st; Rd., Kaohsiung, 81362, Taiwan, Province of China	Jul 17, 2019
TW10005		Yes	Chang Gung Medical Foundation Institutional, Review Board Chang Gung Medical Foundation Institutional Review Board, B2F., No.123, Dinghu Rd., Guishan Dist., Taoyuan, 333, Taiwan, Province of China	Dec 17, 2021
US10006	United States of America	Yes	WIRB, WIRB, 1019 39th Ave SE #120, Puyallup, WA, 98374, United States of America	Jul 29, 2019
US10009		Yes		Jan 15, 2020
US10010		Yes	Univ of IL College of Medicine at Peoria IRB Univ of IL College of Medicine at Peoria IRB, One Illini Drive Box 1649, Peoria, IL, 61656, United States of America	Jun 05, 2020
US10023		No	University of Texas Southwestern Medical Center; IRB/EC University of Texas Southwestern Medical Center IRB/EC, 5323 Harry Hines Blvd, Dallas, TX, 75390, United States of America	Jun 22, 2020
US10031		No	Sterling Institutional Review Board, 6300 Powers Ferry Road, Suite 600-351, Atlanta, GA, 30339, United States of America	Feb 08, 2021
US10032		No	Legacy Research Institute IRB, Legacy Research Institute IRB, TBD, Portland, OR, 97232, United States of America	Sep 08, 2020
US10033		Yes	WIRB, WIRB, 1019 39th Ave SE #120, Puyallup, WA, 98374, United States Of America	Sep 24, 2020
ZA10002	South Africa	Yes	Pharma Ethics (Pty) Ltd, Pharma Ethics (Pty) Ltd, 123 Amcor Road, Lyttelton Manor, Centurion, Pretoria, Gauteng, 0157, South Africa	Jun 18, 2020

EC, Ethics Committee; IRB, Institutional Review Board.

Supplemental Table S4: Additional Patient Quotes

Concept	Quote
Previous Experience with Treatment of PAH	
Patients Who Have Previously Treated their PAH	*"**Of course it** [pill burden] **does**...! [impact my life] You start the day with a stomach protectant in the morning... You take your medication for rheumatic disorders. After that... cardiology is looking at you for this PAH.... **Constantly taking medication into the body was psychologically disturbing for me**. I was also using cortisone at that time. You also gain weight at serious rates. **And this seriously disturbs your psychology**. So... again the medicine... **I was afraid that my kidneys would fail**"* "***I had palpitations, nausea, dizziness, insomnia, body discomfort, restlessness [due to taking all the medications]**. And when I went back, I told them I did not know if it was because I took everything together because I didn't have a set schedule. **I'd make a cocktail of pills, put it in my mouth and take them. So I spent the whole day feeling terrible***" "*It happened quite a lot [impact on daily life] that even the fact of **putting on my socks, or bathing and bending down to clean my feet, that was something that was limiting me more** [sic] and that was **making me sad**, because… **"they are too many pills** and this is progressing fast*"
Knowledge of Combination Therapy	"*They [prescribing clinician] did mention another option but **I believe I would have to take two pills. I wouldn't take just one***" "I'm sure he has…talked to me about different ones [medications] but... **the dual was what he felt was best for me**" *Yes… that mine [PAH] was just starting to require a single medication… **I have a preexisting condition that I knew eventually that I was going to end up having to take medication for this**"* *"**Oh my, there are many** [medications for other co-morbidities], because of Systemic Lupus Erythematosus, there's Metypred…Basically, it's 2, Chloroquine and Metypred. But I also take others, wait…(counting) 10… 11… 13…14" [tablets]* *"…No. **This is the first time I'm getting treatment for it** [PAH]"* *"**Yes, I knew that… there are even 3 therapies in order to treat pulmonary hypertension**… that it works better for us. I mean, the deterioration that we tend to have when it comes to cardiac input is actually progressing as the pulmonary artery pressure increases. Therefore, having 2 therapies helps us, helps us to stop the widening of the pulmonary arteries and avoid right ventricular hyperplasia. **So, it helps a lot having 2 types of treatment together"***
Pill Burden Prior to the DB Portion of the Trial	*"I mean, they're little pieces of time here and there but it's… **actually time-consuming**"* *"**I kept having to remember remembering to take 'em** [tablets]**and remembering how many and what day**…And that part was a little bit overwhelming …But after the first month, like I said, I was good"*

	*"**Making me sad**, because I was like "**they are too many pills,** and this is progressing fast"* *"**It was very bad**, it's much better now. **It was bad because of the time schedule... you're out with a small child, so sometimes the timing didn't match up**. I don't think I forgot because I was able to take it properly, but it's very complicated… **you have to take it three times a day, early in the morning, late at night, it's not very good, the results were good, but it's bad to take medicine every eight hours**"* *"Of course, it [pill burden] does! [impact my life] You start the day with a stomach protectant in the morning... You take your medication for rheumatic disorders. After that... cardiology is looking at you for this PAH.... **Constantly taking medication into the body was psychologically disturbing for me**. I was also using cortisone at that time. You also gain weight at serious rates. **And this seriously disturbs your psychology**. So... again the medicine... **I was afraid that my kidneys would fail"*** *"So I always decided, because I had to take them all at the same time. Like, always, every day, **I decided to always take them at 9 am.** So there was no problem for me, because **when I took it, it was in sequence, three to four pills every day, at the same time**"* *"So there was a matter there that I didn't have a fix schedule because **I always wanted to have something in my stomach before I take the drug. And my family helped me a lot. They knew, if I was… close to forgetting they were like "you can take your drugs now that you have had breakfast"*** *"**That was rough**. It took me a little bit to adjust [to take so many tablets]. **I had to put a reminder in my phone**"*
Adherence Prior to the Clinical Trial	*"it's **very important** [to make sure they take the PAH treatment]"*
Treatment Experience During the Double-Blind Period	
Experience Taking 4 Tablets	*"…**The fact that there were four, and not just one**. Cause **I had to repeatedly punch them out and keep them all together…**., and when I would travel, I had to take, you know, extra, it was extra volume to my suitcase, so I guess **that kind of annoyed me**"* *"Well, at first**, I didn't understand how it was possible to take all four tablets together,** but I got used to it. That it was too much medication to take at once…Too much medication…**Not convenient, because I was afraid, I would choke on them**…As I suffered from esophagitis, I felt that I would choke on them"* *"**...I was always stressed out thinking that I would take it [study medication] carry it with me or forget it when I went somewhere**. When I went out of the house, I had to check my bag all the time. Did I put it there or not?!.... **When I went out, when I went on vacation, when I went on a long journey, I had to keep it in my mind all the time.** Even if I had to go somewhere urgently, **it was always in my mind. Whether I took it [study medication] or not, whether I had it with me"***

Management of Taking 4 Tablets	*"It was **just the thought that made me a little bit dissatisfied, am I now getting the PAH** drug, or am I in the blind study [placebo], that is, in the part of the study that is not receiving any drug"* *"Health, you know... when you take a medicine, you think it will make you better, it will cure you. When you take an antibiotic or a painkiller, it takes away your pain. **I said, no, this medicine will make me tired. It's not like my previous medicines**. I was thinking that I was getting more tired"* *"**I'd say it's easy** [not to miss a dose]. **Sometimes,** I don't know, **I think I've even taken it** [study medication] **twice a day because I worry so much and there are so many pills, right?** So what do I do? I separate them. I leave it in a corner, on the table. And then I know I have to take it. **Then when I take it, I put it away. So, I don't forget whether I took it [study medication] or not"*** *"Well, [talking about change in lifestyle] you have to time yourself according to it, **of course, so you have to keep the time** [for administering the medication] ...**Well, you always have to eat breakfast at the same time in the morning and then take the pills**"*
Ease of Taking Double-Blind Medication	*"But as far as remembering to take them, that was not really a big deal, 'cause **I do take them at breakfast, and I always eat breakfast**"* *"**Since it was at a fixed time, and I only had to take it** [medication] **once**, to me it's just taking one pill or four pills at one time**. I don't think there was much difference** [remembering to take the study medication]"* *"**I had to constantly remember to put it** [trial medication [4 pills]) **in my bag when I left the house**. Like this.... **So I knew I shouldn't forget i**t. That's why I had to put it in my bag when I was going somewhere... **It was just stressful for me** [to remember to take the trial medication]"* *"**When I had more than one pill, I carried the entire sheet. The one you gave me** [instructions on when and how to administer study medication], **with all the pills on i**t. **I carried it with me, and I could see which day and which ones I took and which ones were left**"* *"They [clinician] told me **I had to take them at the same time**, after an hour you can eat... **and all of the instructions, which I follow**" [to aid remembering to take study medication]"* *"So I always decided, **because I had to take them all at the same time**. Like, always, every day, **I decided to always take them at 9 am. So there was no problem for me, because when I took it, it was in sequence**, three to four pills every day, at the same time"* *"**I don't feel that I've had any problems with them**"*

	"I've been chronically ill for 15 years, ***so I'm simply used to taking medications****. I previously had issues with arterial hypertension in general,* ***so I always took a lot of medications. Now, in fact, I have more****. As I said,* ***I've been taking medicines for 15 years, and for me, it's not a problem*** *[remembering all the tablets]"* *"Nothing [impacted the act of remembering to take study medication].* ***Just as usual, nothing much. I have to treat my illness.*** *I have to take the medicine.* ***I put it in the medicine box, which lasts one week. I put it in, the amount I take today, I put it in the medicine box, and remember to take it in the morning****"* *"****Well, …it was easy*** *[remembering to take the study medication]* ***because the only thing that I had to consider was the matter of eating. I did take them before*** *[eating] once or twice,* ***but mostly I took them after eating****"*
Adherence to Clinical Trial Medication	*"…As far as …having to take four [study pills] of them,* ***I guess …I figured that was just part of the study"*** *"I was happy [taking the multiple tablets] because, as the medicine worked fine,* ***I didn't see any problem because it was working fine for me honestly. I was so bad, and the medicine was working, so I was happy****"* *"****It was actually making me feel better by taking them*** *and knowing that I was doing something to help my actual breathing and everything"* *"****It was just the thought that made me a little bit dissatisfied, am I now getting the PAH - drug, or am I in the blind study, that is, in the part of the study that is not receiving any drug****"* *"****At the beginning when I took these 4 tablets, again I felt tired****. I thought at first that it was not going to help me…****I didn't think it would be very good for me****"*
Treatment Experience During the Open-Label Period	
Positive Experience Taking Single M/T FDC Treatment	***"It's way easier. It's a lot easier*** *[taking 1 tablet].* ***And I don't have to… follow a book,*** *I just…* ***open the bottle and… take one*** *[laughs]"* *"****So now it's one pill for everything and for me it's been much better, and in a way*** *I felt even better than when I was taking the [other] three pills.* ***So it's getting better and better for me****"* *"****It was really a relief to only have to take one tablet now. I enjoyed it*** *(laughs). The package was not difficult to open, it was in a little box"* *"When I started to take those medicines [M/T FDC] and the doctor stopped my other medicine [4 tablets], and* ***I felt like so good****. … "****I was like, "You know, I just have to take one tablet, phew"***

	"Because I have not experienced any relapse after taking the medicine of the first and second parts, ***I feel that taking only one pill in the second part is more convenient, practical, better and satisfactory****"* *"The* ***fewer the tablets****, it's always* ***better****"*
Continuation of Taking the MT/FDC Treatment	*"****Yeah. It's really nice to take only one tablet-*** *Yes. So many times, I just wanted to tell the doctors like, you know,* ***"I don't want to take all these tablets now"*** *"****I would honestly be ecstatic*** *[to continue taking the single tablet].* ***…A lot easier to fit just one pill for something… into my rotation or my schedule****. ...I wish I could do that for all of my stuff"* *"****I do*** *[want to continue] and* ***I'm really worried that I won't be able to continue,*** *you know? Even if I face all the exams again, maybe even the catheterization, maybe I'd have to face them again. That catheterization is painful as hell, but not me.* ***I'd rather face it all again and start all over again than go without treatment, you know?*** *It's like that for me"* *"Well, yes, because now next year… my period will come to an end, and…* ***I would really like to keep taking it because… the quality of life that I have now with this pill… it really worries me losing that****. Because of the lack of treatment"* *"****Because with this drug I can breathe better, I can feel the mobility in my life better, I can walk faster,*** *maybe if I go back to my old drug, it won't tolerate me as much, ...****So, it's really good for me. I can climb stairs. I don't rest when I climb stairs anymore****. You know, it's very rare. I can walk fast. Even pace sometimes.... For example, I give an example,* ***think of 1 km or 1 meter, I say I can run half of that. I have this self-confidence in myself now. That's why I want to continue this medication if the study ends****"*
Pill Burden in Open-Label Portion of the Clinical Trial	*"[Important] Because the feeling of sickness is not so strong then. The sick feeling, by that I mean you need so many pills to stabilize that.* ***If I just take one tablet, then it just feels better****"* *"Oh, yeah, definitely [prefer the single tablet]. Taking fewer tablets makes me feel like ...a more normal person.* ***The more pills I take, the more I think I'm chronically ill; it's just a reminder of my illness****"* *"****It just makes it, I don't know, like I feel like taking one pill compared to three or four makes me feel like, I don't know, I'm not as bad as (laughs) I think I am health wise****...'Cause before when it was like three or four, I was like,* ***"Man, I really must be really terrible health-wise. (laughs) If they're making me take three or four"*** *"****Of course, it's better to have fewer tablets****, you have fewer boxes, you have less in the can. Of course,* ***that's already easier, to take only one tablet instead of three****?"*

	"Well, I think… it's very good. I mean, ***if this is going to work for my health****…* ***and it's only one pill… then that's great****"* *"It's comfortable.* ***It's comfortable to take that pill*** *…. Well, it was a lot of medications and with this one the* ***truth is that as side effects that I've had that I could mention would be very few, with macitentan and tadalafil. For me, it has been great****"* *"****I am very happy with it*** *[1 pill]. I'm very happy...****One dose. It doesn't tire me at all.*** *Just like that"* *"Sometimes …you just take...* ***If you have to take 10 pills at once, it's really, really draining, it makes you don't wanna take your pills****. Sometimes you just, "Ah! I don't wanna take this pills, they are so many."* ***But if you take five instead of 10, it's better****"*
Adherence to Clinical Trial Medication	*"****…It's easier to remember*** *and to actually fill my pill containers****… it's easier for me to plan for the week, especially in the morning****, with getting ready for work"* *"Now, I usually take them in the morning, so I have an organizer with all the pills.* ***And the ones from you for pulmonary hypertension I have them in a separate, smaller one****"* *"…It simplifies things. It simplifies my life****. It is …much more convenient, and, …it gives me confidence that I'm doing something good for myself****"* *"****It's easy, I just have to put the medicine in the box****, and every morning, after I have my meal, I have to remember to take the medicine out quickly"* *"It is easier for me to remember in the morning. Because you have not had breakfast yet* ***so when the time comes, you take everything so there's no mistake****"* *"Well, it's better to take one, right? Rather than 4 and having to remember the timings.* ***Because as I mentioned, even if you go out or meet friends or family, you don't have to remember and keep track of taking the pill****"* ***"I have already a routine*** *[for remembering to take medication] and…* ***I wake up, have breakfast, my pill, you know****?* ***Once I had my routine stablished, I already… And as it is working fine, I don't forget to take it. That's for sure****"* *"You rush …to go to work, and you think of all the tablets****… this is one tablet. You just take it quickly and you're out"***
Adherence to Single FDC Tablet in the real world	*"Well, that's a lot better [taking 1 pill].* ***It's easier…makes it easier with just having to take one"*** *"****Much better*** *[adherence to 1 pill].* ***Because I think that in this phase it's easier*** *[open label]. Even though sometimes I have doubts,* ***it's much easier with just one, you know?"***

	*"**I never missed it** [taking the study medication]"* *"**Well, it's better to take one, right**? [Rather than 4 [pills] and having to remember the timings"* *"**The fewer the tablets, it's always better** [for adherence]"* *"No, **I always take this** [1 pill] every day"* *"No. **I just don't forget to take it,** as I mentioned**. I take it every day at the same time. I don't forget"***
Further Patient Perspectives on Treatment	
Mental Health Benefits of Taking Fewer Tablets	*"**Well, it would mean… wellbeing**. Because then **I wouldn't need to be thinking about what I have to take**"* *"**Oh, psychologically, I think it would be a big boost**. …Every pill makes me a little bit more sad that… I'm sick, and **it's just a … daily reminder that I'm sick, and having fewer pills just makes me feel better about myself**"* *"It's a good thing. **Psychologically it's a good thing**. …**Now I'm taking one pill instead of three or four.** The brain tells you …it's better. I feel better. I'll tell you that. **It's better for me**"* *"**Constantly taking medication** into the body was **psychologically disturbing for me**"*
Patient Endorsement of Continuing the Medication After the Trial	*"**I do** [wish to continue treatment] and **I'm really worried that I won't be able to continue, you know?** Even if I face all the exams again, maybe even the catheterization, maybe I'd have to face them again. That catheterization is painful as hell, but not me. **I'd rather face it all [tests] again and start all over again than go without treatment, you know? It's like that for me"*** *"**Yes, I'd like to** [continue MT/FDC treatment] …because it works fine. **I observed a noticeable improvement since I started taking these pills…I'd like to continue taking them**"* *"**Yes, yes. I'd be very pleased to keep taking macitentan and tadalafil**…Because I know it's a good therapy. I know that both macitentan and tadalafil are good in response to pulmonary arterial hypertension."* *"**It certainly is** [a medication to carry on taking] …**Because with this drug I can breathe better, I can feel the mobility in my life better, I can walk faster**…I don't rest when I climb stairs anymore…think of 1 km or 1 meter, I say I can run half of that. **I have this self-confidence in myself now**"* *"**Yes. I want. I will continue** [with MT/FDC post clinical trial] …Because… I'm feeling… so much better…**It made my life… so nice. I can walk properly, do my work, everything**"*

What does Ideal Treatment Look Like?	*"I'd want to get **just one pill**"* *"**…One pill a day, …maybe even one pill a week would be better**. ...It doesn't have to be a daily reminder"* *"... [my ideal treatment] **Probably the way it's going right now** [during the open-label period]. ...I don't have any issues, that's pretty good treatment. ...I can't complain…. **I don't have any issues with it. I prefer the one compared to a bunch**"* *"I would think that taking oral medication is simpler and able to control it. **So I would prefer to just take oral medication, why bother trying other treatment methods**"* *"Normally, **the ideal treatment would be no medication at all**, **but right now one pill is ideal for me**. Or **it could be one dose a month. It could be an injection. That would be ideal for me.** It would be more **comfortable to get a shot once a month and not think about it for a month**"* *"How I'd like it? [on ideal treatment] **I'd want to get just one pill**"*
Preferred Mode of Administration for PAH Medication	*"**For me, I'd be happy in the same way. One pill, even oral**, whatever, you know?"* *"No, well… **I would prefer the oral one**"* *"Oh, no, **I would not like to receive intravenous treatment**… I have never received it. **I am used to taking tablets**"* *"**Yes, oral medication**, because chronic diseases need to be improved gradually. **It is still necessary to take oral medication, not by injection**. That's the way"* *"**…The least amount of …pills possible. No IV medication or anything like that.** And just, you know, morning and night pills. **Once a day or twice a day is the best"***

DB, double blind; FDC, fixed-dose combination; IV, intravenous; M/T, macitentan/tadalafil; PAH, pulmonary arterial hypertension.

Supplemental Table S5: Additional Clinician Quotes

Concept	Quote
Typical Approach to Treating patients with PAH: ESC/ERS Guidelines	
Clinician Awareness of ESC/ERS Guidelines	*"**We try… to follow the international guidelines, the European guidelines**. So, **we start with combination treatment, …almost in all of the patients… that present in functional class 2, 3, and in an outpatient setting"*** *"**A nice suggestion [is] to add to [the ESC/ESR] guidelines additional information that the treatment should be started from… fixed dose combination.** Now, we have evidence suggesting that… this formula is resonate well. And then should we add it …to guidelines"* *"So we knew that**… these therapies were recommended for …standard of care many, many years ago**"* *"Yes, I know. If there is comorbid cardiopulmonary disease, then monotherapy. If there is no comorbid cardiopulmonary disease, then combination therapy is recommended from the initial period. For the low and moderate risk group... **the guidelines suggest ambrisentan tadalafil or macitentan tadalafil, but if the patient is in the high-risk group, the guidelines emphasize that we should start with a triple combination with IV prostanoids**"*
Clinician Initial Approach to PAH Therapy	*"…**Typically, upfront dual therapy, unless there were comorbid conditions that would preclude doing so** – And, …again, depends on the patient's, …underlying functional status and risk"* *"**We try …to adjust our therapy from the beginning to combination therapy**. So …nowadays, …**it is the most common… therapy we use, combination therapy from the beginning**."* *"**I prefer… duo-therapy because, according to guidelines …in patients with intermediate and high risk, we have to start with combination therapy.** I prefer monotherapy only in patients with… cardiopulmonary comorbidities or in… fragile patients, like low blood pressure or … some mild cardiopulmonary problems like that. Normally…I prefer the combination treatment"* *"**As they become symptomatic, they're more advanced in their disease process, so typically, if they have… some moderate… risk factors, I tend to use… double oral therapy**…in terms of a PD5 and an ERA."* *"**So those [PAH] patients, unfortunately, we could get them on no drug…, because the… cost of access to those drugs were, one, prohibitive**. And secondly…, they've just been recently registered in the country… for management in those particular situations. **So we had very little access… previously to those particular drugs**"*
Monotherapy as Initial Approach to PAH Therapy	*"**…Initially we would use monotherapy. But if a patient then… low risk, then we would… do the sequential double therapy or triple therapy combination therapy. But some of patients is, critical patient, maybe… functional** test*

	four…so… we would apply two medications or three medications at the same time. ***But… it's important to - because this medication is… expensive so you still have to get approval from the National Insurance****"* *"It…* ***depends a little bit, for example, if the patient has low blood pressure or so… then we start, for example, tadalafil with 20 mg, and if the tolerate 20 mg****, then we… tell* ***the patient to should… increase to 40 mg within the next week, and then we start the second drug,*** *for example, macitentan 10 mg"*
Clinician Feedback on M/T FDC During Clinical Trial	
Positive Feedback on M/T FDC During Clinical Trial	*"Obviously taking one pill as opposed to two is easier on the patient.* ***But I didn't have missed doses [in my patients]"*** *"I am saying what I have observed. Everyone has their own...* ***It is more advantageous to take one pill than two pills, if you take the same pill"*** *"****…I have a very positive opinion*** *[of M/T FDC]."*
Clinician Interpretation of Treatment Satisfaction for Patients	*"****Patient adherence will be significantly better… if patient will still…see a lower number of pills on his hand every morning****."* *"****They [patients] liked just… the single tablet for sure" and "I think it*** *[M/T FDC]* ***was excellent. At least from what our patients reported****"* *"****They're [patients] just happy that it's just one pill*** *[M/T FDC] they have to take, as opposed to two [or more]"* *"****…Easier adherence… to therapy*** *[with M/T FDC]"* *"****I believe that it [M/T FDC] will improve adherence…for the patient and will make their life easier****. They have to take* ***less*** *pills"* *"****If you reduce a pill burden in a patient who's taking at baseline… five or six tablets… it makes a big difference"***
Real-world implications of M/T FDC	*"Two brand name drugs together as one tablet.* ***Hopefully, they can argue, you know, kind of make it more affordable …to the carriers and the patients.*** *But yeah, definitely, that's always… the most difficult thing in the PAH world is getting drug… approved [by the patient's insurance]"* *"I think* ***we would move to prescribe the single tablet in most of our stable patients****"* *"****Yeah… so we would definitely use it*** *[MT/FDC]. I mean, we would roll it out.* ***It's now regarded as a standard of care in a patient with PAH, right?****"*

	*"I think... **Dual combination is superior to monotherapy. So yeah, I think those, those patients would definitely benefit from this** [M/T FDC]"* ***"I think it would be appropriate** [administering MT/FDC to wider population]. **I mean, the two most used drugs in the PAH community, in the treatment. So I think it would be appropriate. I think it would be positive**"* *"**Yes, actually, I have… many fixed-dose prescribed medication**, … easy [for] patients control it **because a patient always complains to us, too many pills"***
Perceived Benefits of M/T FDC for the Wider Patient Population	*"**Anecdotally we did have patients that were a little bit distraught at the concept of having to go back to multiple pills a day** at, at completion of the study. So… I think **the patient-centered side of things… there was a lot of benefit… psychiatrically…, for the patients**"* *"**Well, I think it will be absolutely suitable [for everyone]**, and it will be… an interesting improvement…**if we can offer them a combination in a single tablet... this is positive, of course**"* *"**The benefits… it's… once a day**. …The comparator, if you take sildenafil, it's three times a day. …You know… it's a very nice regimen for patients. **They [patients]can take one tablet once a day, it's one less… stress for them [patients]**"* *"For me… I think it's [MT/FDC] **really revolutionized the management** [of PAH]"* *"There are advantages. I did not see any disadvantages... Big tablet, difficulty in swallowing, etc..... there will be advantages of it... Only, maybe, if two of them are taken together ...**I mean.. actually I do not think it will happen**.... macitentan is not very effective on blood pressure. I wondered if there would be a sudden hypotension when both are taken together, but I don't think so. **I think taking a single dose will definitely have a positive effect, increasing patient compliance**"*
Potential Drawbacks of M/T FDC for the Wider Population	*"**The most difficult thing in the PAH world is getting drug… approved** [by the patient's insurance]"* *"**Every new medication that comes down the pipeline you're gonna have issue upfront probably with insurance coverage**"* ***"If I had access to this drug for all my patients at a reasonable rate, I would definitely use it**. Our… limiting factor, again in South Africa is the cost of the drug"* *"…Really **the lower socioeconomic status…patients that… struggle** with taking meds… those are **the kinda patients… that are most… suited for it"***
Suitability of M/T FDC for Treatment-naive Patients	

Clinician Perspective on Impact on Future Prescribing Practices	*"**You have adverse events**, and you don't know **do the adverse events come from drug A or from drug B**"* *"**That's right, 100% appropriate** [prescribe MT/FDC as a first line approach for treatment naive patients] … **the survival efficacy** and morbid-related disease, **disease-related complications are low, as the sooner the more effective for naive patients**"* *"**Oh, sure**. [prescribing MT/FDC as first line approach to treatment naive patients] **That's… for sure**. **That's… what we're doing with… two different… the two pills**, let's say, the… two drugs"* *"**Yeah. Absolutely** [I would use as a first line treatment], **most of my patients in naive get the combination,** but as separate pills"* *"**Sure** [I would use this with naive patient], **yeah. I mean, that's, that's the go to medications I use anyway**"* *"**I think we would move to prescribe the single tablet in most of our stable patients** [if it was approved]"* *"**Yes, according to a study, which has already demonstrated for naive PH patient, the upfront combination therapy works better… than monotherapies**. And therefore, **the guidelines already recommend for the naive PH patient, we should consider upfront combination**"*
Clinician Perspective on Prescribing M/T FDC as a First-line Approach to Treatment-naive Patients	*"**At first, we have to start with one drug**, and… then we give a couple days later the second drug. **So that the body can… … learn which side effect come from which drug**, and they [patient] **can adapt to these side effects**"* *"**We wait for at least a couple of weeks, just to check everything is okay, and there are no secondary effects, and then we add the second one**, just to understand if any secondary effect should appear to distinguish, which is the responsible drug. **So after this up titration period … We can call it like that... The single tablet… will be great**"* *"…I think…, if the patient…, [inaudible] three or four week, we can use… the authority in the first time. But because the [location] National Health Administration… limitation, **so we cannot use two medications on the first time. So we have to try …one medication and sequentially to add the other medication**. So maybe initial, we use a monotherapy, but later... we can apply the fixed-dose [inaudible] so we can still use the [inaudible] fixed-dose on this kind of patient"*
Clinician Perspective on Health-Related Quality of Life Improvement for Patients Taking M/T FDC	*"**I think they will improve outcome and quality of life**, view to a better… treatment…Like, in our experience of the clinical study…many of these patients had at the end… in the open label phase, a normal right heart function or a normal size of the right heart. **The right heart has improved**. And that means the right heart can pump better, and the patient can do more exercise and…so they feel better, **they have… less symptoms, and they will live longer**"*

	*"**It definitely improves** [quality of life]. ...**I mean, you know, if you ask anybody if you want to take one pill versus two (laugh), they'll say, "I wanna take one."** ... **I think that by itself improves the quality of life**. ...And then these days, believe me...**, the patients, especially our younger patients… who have high copays and have to go through charity and whatnot… will really appreciate that one answer of… they are not going to run out of their medication**"* *"So we try once day is better. Twice daily... is better than three times daily or four times daily. So it's other relation. And of course..., just look, **it's reduction in the number of pills… per day. …Its additional element modifying, of course, positively modifying the quality, quality of life**"* *"**And maybe some patient will have this psychological effect of, well I'm taking less pills.** That's... what I think".* *"They feel better and they, they are, **their quality of life will be better**"* *"As I mentioned before, because... **a patient take a medicine regularly so they can improve their disease status**, so... **they can make their disease controlled basis**"*
Adherence to Single FDC Tablet	
Clinician Perspective on Adherence to Single FDC Tablet	*"**No, it'd increase adherence yeah, it would help improve adherence**"* *"**I think it** [adherence] **will improve**"* *"**…My only concern would be for** [pharmaceutical companies] to get it in at a price that would be of parity."* *"**…Well, they should receive it as a positive impact**. They would take not so many pills"*
Clinician Perspective on FDC Treatment Adherence in a Real-World Setting	*"**For everyone, patient adherence will be significantly better… if patient will still… see a lower number of pills on his hand every morning**. ...We are sure for this. **…Moreover, some people they think that "Oh, I'm more ill because I see more pills on, on my hand**", especially males. It's a typical problem... for males because... pulmonary hypertension... is of course one"* *"**I think about all the patients that I've seen with PAH, invariably they've all got some additional pathology and… per burden is significant problem for them…So if you can reduce their upper burden any way whatsoever, I think it'll definitely improve adherence**"* *"[adherence] ...I think it depends on... the background and cause of their disease process. I think we all know that ...**drug and toxin associated patients… can be difficult in terms of… adherence to therapies**, just addiction is difficult and so ...it's a whole other issue"*

	*"**Not only that the patients' adherence improves**, it also **improves the description of both drugs by… the medical… advising of the doctors**"* *"Since combination therapy is recommended to achieve the necessary response, **in that sense, taking a single drug instead of taking two drugs will definitely increase compliance** [in a real-world setting]"*

ESC/ERS, European Society of Cardiology/European Respiratory Society; FDC, fixed dose combination; IV, intravenous; M/T, macitentan and tadalafil; PAH, pulmonary arterial hypertension.