23 de agosto del 2021
CEC-ICIC-C0620-2021

Doctora
Priscilla Umaña Rojas
Presidente Suplente
Consejo Nacional de Investigación en Salud (CONIS)
Ministerio de Salud
Presente

CEC-ICIC-E096-2018 Investigador Principal: Dr. LihTeh Wu Tseng
AQUILA: Estudio observacional prospectivo en pacientes con degeneración macular húmeda relacionadaa la edad o edema macular diabético para evaluar la frecuencia de uso de aflibercept intravítreo, en la práctica clínica de rutina en América Latina

Estimada Dra. Umaña:

De acuerdo con lo indicado en oficio CONIS-203-2021 del 21 de mayo del 2021, mediante el cual se solicitó el registro de las publicaciones de las investigaciones finalizadas de acuerdo con el inciso t) del artículo 48 de la Ley No. 9234 "Ley de Investigación Biomédica", me permito remitir copia de la publicación que nos han llegado del estudio citado y la actualización del cuadro de publicaciones.

Atentamente,

JESSIE MARIA ORLICH MONTEJO (FIRMA)
Digitally signed by JESSIE MARIA ORLICH MONTEJO (FIRMA)
Date: 2021.08.24 07:42:06 -06'00'

INSTITUTO COSTARRICENSE DE INVESTIGACIONES CLÍNICAS
COMITE ETICO CIENTIFICO CEC - ICIC

Dra. Jessie Orlich Montejo
Directora

c: Archivo
JOM/smg.*

ANEXO No. 1

PUBLICACIONES ESTUDIO

CEC-ICIC-E096-2018

Intravitreal aflibercept for the treatment of patients with diabetic macular edema in routine clinical practice in Latin America: The AQUILA study

Francisco J. Rodriguez,[1] Lihteh Wu,[2] Arnaldo F. Bordon,[3] Martin Charles,[4] JinKyung Lee,[5] Tobias Machewitz,[5] Margarete Mueller,[5] Gabriela del Carmen Gay,[6] Jans Fromow-Guerra[7]

[1]Fundación Oftalmológica Nacional, Universidad del Rosario School of Medicine, Bogotá, Colombia; [2]Asociados de Macula, Vitreo y Retina de Costa Rica, San José, Costa Rica; [3]Hospital Oftalmológico de Sorocaba, Sorocaba, Brazil; [4]Centro Oftalmológico Dr Charles, Buenos Aires, Argentina; [5]Bayer AG, Berlin, Germany; [6]Bayer SA, Munro, Argentina; [7]Macula Retina Consultores, Mexico City, Mexico

Presented at European Society of Retina Specialists (EURETINA) Virtual Meeting, September 9–12, 2021

AQUILA (NCT03470103) study design

Purpose: To evaluate the clinical effectiveness (functional and anatomic outcomes) and safety of IVT-AFL in patients with nAMD or DME in routine clinical practice in Latin America

Patients: Aged ≥55 years with nAMD or aged ≥18 years with DME, treatment-naïve or previously treated

Treatment: IVT-AFL per routine clinical practice and following local prescribing recommendations

Primary endpoint: Mean change in BCVA from baseline to Month 12

[a]AQUILA nAMD data will be presented at EURETINA 2021 in the presentation titled "Intravitreal aflibercept for the treatment of patients with neovascular age-related macular degeneration in routine clinical practice in Latin America: The AQUILA study".

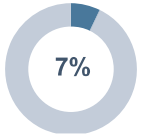
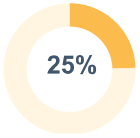
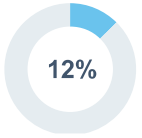
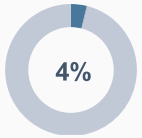
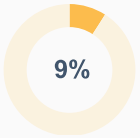
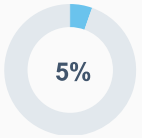
BCVA, best-corrected visual acuity; **DME**, diabetic macular edema; **IVT-AFL**, intravitreal aflibercept; **nAMD**, neovascular age-related macular degeneration.

Patient baseline demographics and disease characteristics

	Treatment-naïve DME (n=181)	Previously treated DME (n=77)	Overall population DME (N=258)
Age, years	**64.6** ±9.8	**63.0** ±8.6	**64.1** ±9.5
Female, n (%)	70 (**39**)	43 (**56**)	113 (**44**)
Country, n (%)			
Argentina	111 (**61**)	25 (**32**)	136 (**53**)
Colombia	11 (**6**)	7 (**9**)	18 (**7**)
Costa Rica	3 (**2**)	6 (**8**)	9 (**3**)
Mexico	56 (**31**)	39 (**51**)	95 (**37**)
Diabetes mellitus, n (%)			
Type 1	18 (**10**)	0	18 (**7**)
Type 2	163 (**90**)	77 (**100**)	240 (**93**)
Severity of DR, n (%)			
Mild	26 (**14**)	10 (**13**)	36 (**14**)
Moderate	66 (**36**)	23 (**30**)	89 (**35**)
Severe	76 (**42**)	40 (**52**)	116 (**45**)
Missing	13 (**7**)	4 (**5**)	17 (**7**)
BCVA, ETDRS letters	**54.5** ±19.4	**52.9** ±18.6	**54.0** ±19.2
BCVA letter score, n (%)			
≥70 letters (≥ 20/40 Snellen)	50 (**28**)	17 (**22**)	67 (**26**)
<70 letters (< 20/40 Snellen)	131 (**72**)	60 (**78**)	191 (**74**)
CRT, µm	**388** ±145	**423** ±146	**398** ±146

Full analysis set; data are mean ±SD unless otherwise stated
CRT, central retinal thickness; **ETDRS,** early treatment diabetic retinopathy study.

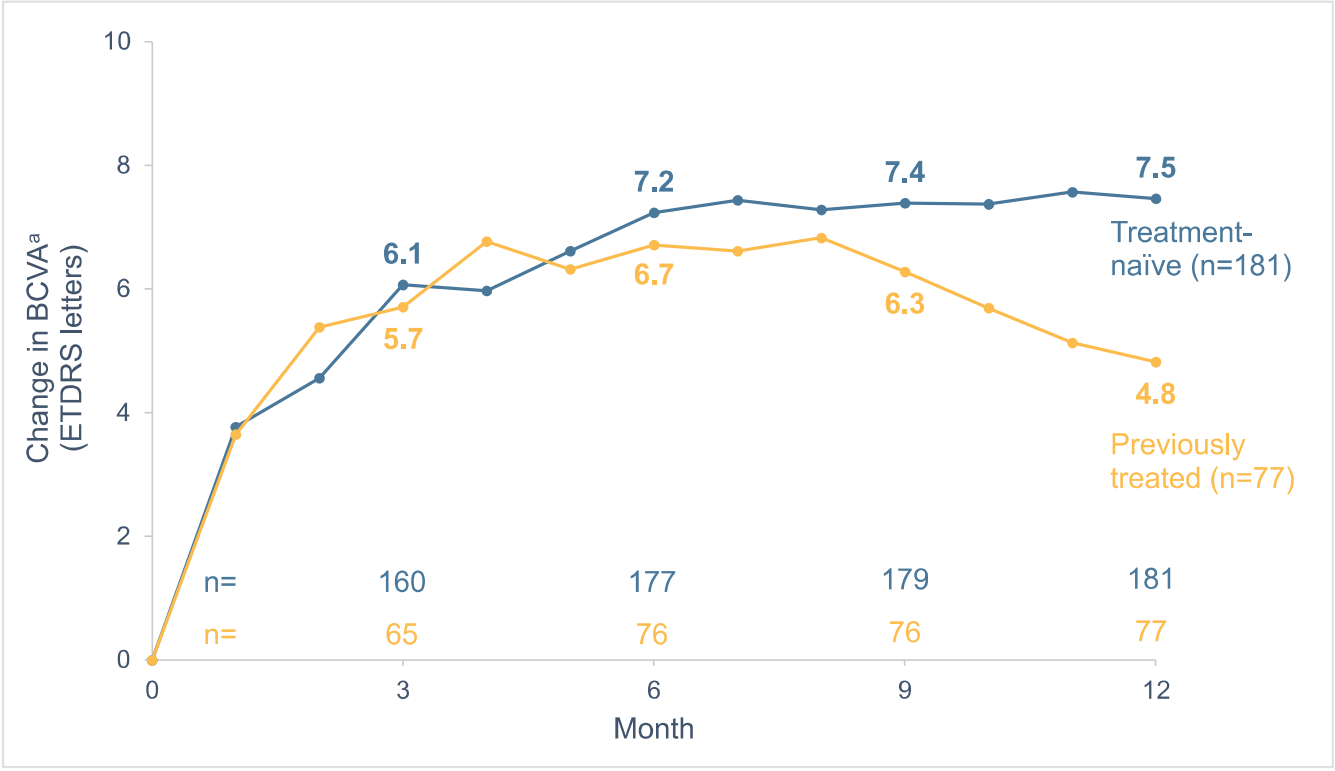
Treatment exposure

IVT-AFL injections	Treatment-naïve DME (n=181)	Previously treated DME (n=77)	Overall population DME (N=258)
By Month 6	**2.9** ±1.2	**3.2** ±1.6	**3.0** ±1.3
By Month 12	**3.7** ±1.8	**4.0** ±2.2	**3.8** ±1.9
≥5 within 6 months			
≥8 within 12 months			

Although the number of injections that a patient received **can be related to efficacy of treatment**, the low number of initial monthly injections, particularly in the treatment-naive patients, suggests **barriers to optimal anti-VEGF regimens** in Latin America

Values are mean ±SD unless otherwise stated.

Change in BCVA letter score over 12 months



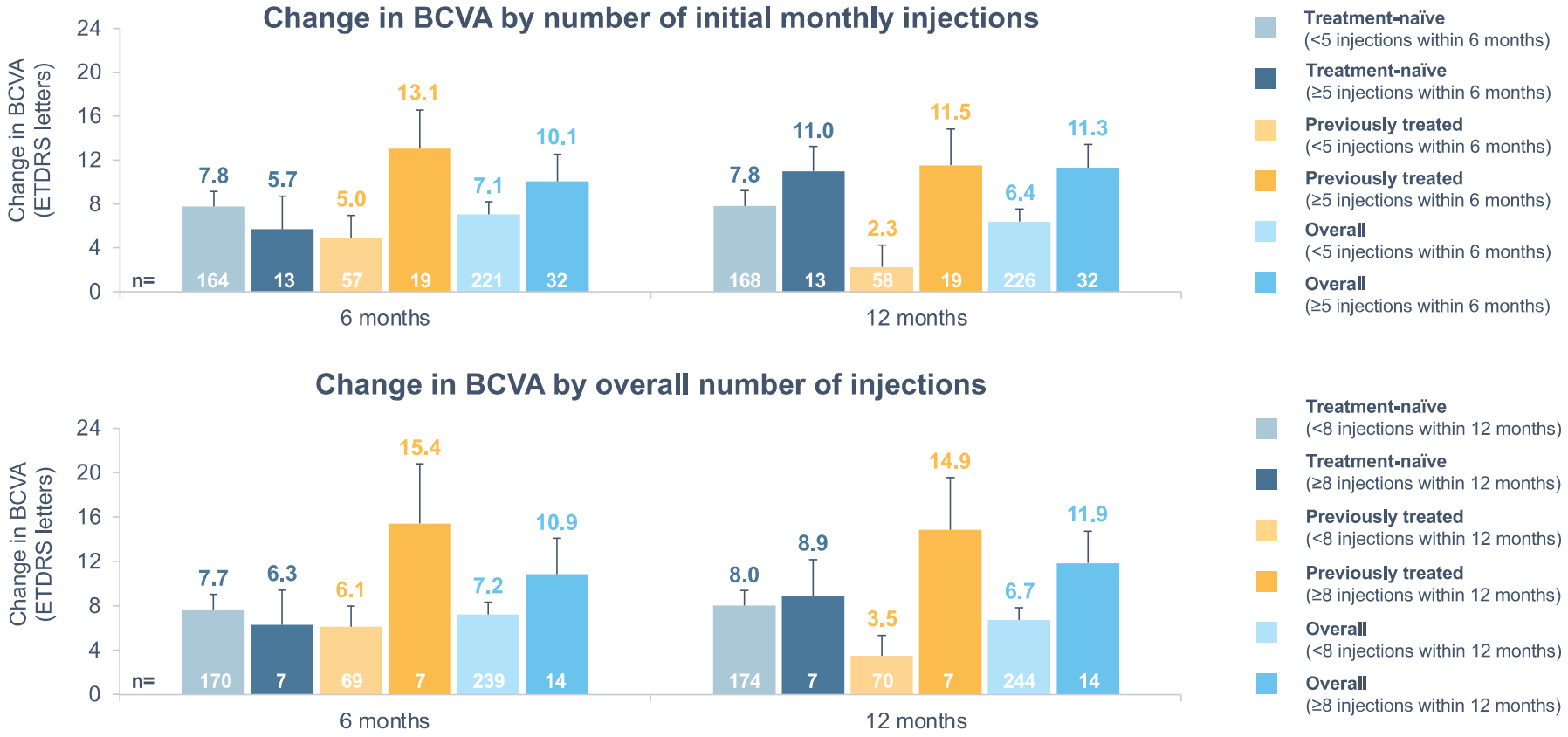
By M12, mean BCVA[b] improved **+8.1 letters** in treatment-naïve patients and **+4.6 letters** in previously treated patients

By M12, there were improvements of **≥15 letters** in **35%** of treatment-naïve and **27%** of previously treated patients

Overall proportion of patients with BCVA **≥70 letters** increased from **26%** at BL to **45%** at M12

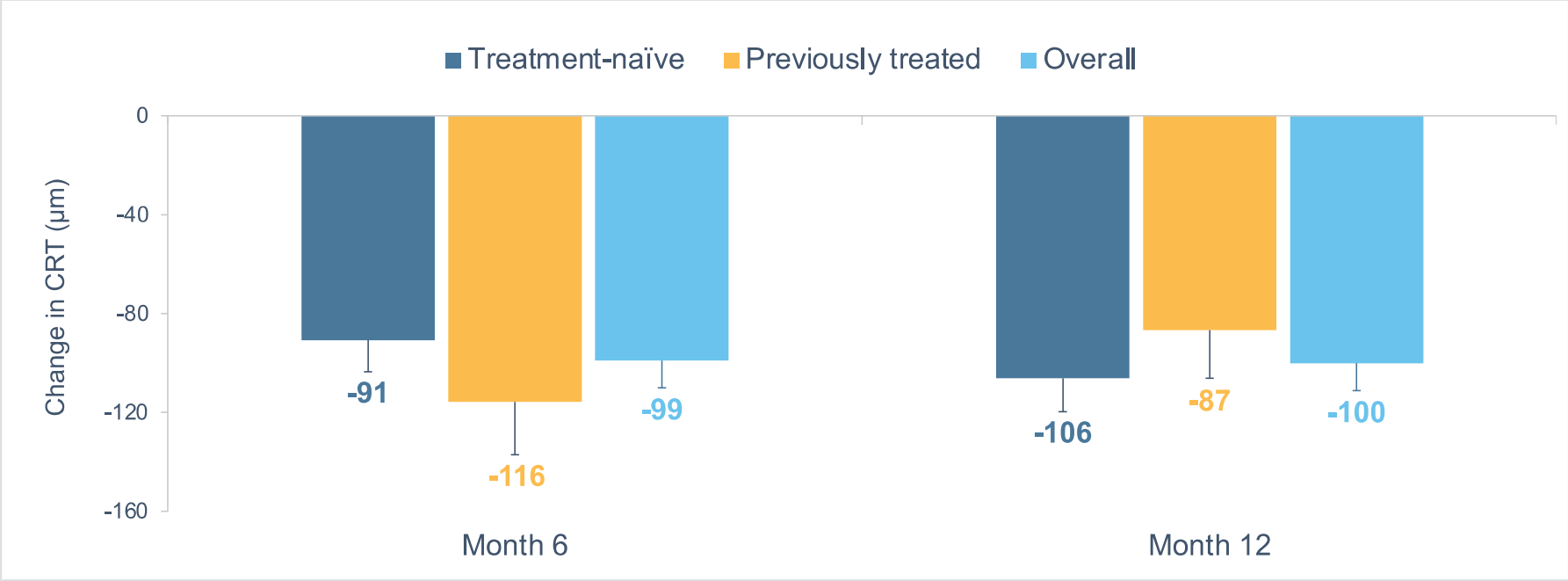
[a]Data were collected monthly ±15 days. [b]Data were collected at 12 months ±60 days; mean ±SD BCVA improved from baseline to M12 by +8.1 ±17.7 and +4.6 ±15.4 letters. Full analysis set; missing data imputed using LOCF.
BL, baseline; **LOCF**, last observation carried forward; **M**, month.

Change in BCVA letter score by number of injections



Full analysis set; data are mean ±SEM.
SEM, standard error of the mean.

Change in CRT at Month 6 and Month 12



The reduction in CRT at Month 12 was numerically greater in treatment-naïve patients

Full analysis set; missing data imputed using LOCF. Data are mean ±SEM.

Safety summary[a]

Number of patients (%)	Overall population (N=319)
Any adverse event	42 (**13**)
Ocular adverse events[b]	30 (**9**)
Vitreous hemorrhage	8 (**3**)
Worsening of diabetic retinopathy	6 (**2**)
Cataract	3 (**1**)
Glaucoma	3 (**1**)
Ocular serious adverse events	6 (**2**)
Ocular treatment-related adverse events	6 (**2**)
Non-ocular adverse events	16 (**5**)
Non-ocular serious adverse events	12 (**4**)
Non-ocular treatment-related adverse events	0
Death[c]	7 (**3**)

There were no cases of endophthalmitis or retinal vasculitis reported

Safety analysis set. [a]Adverse events are those reported if they started after 1st IVT-AFL injection and not later than 30 days after last IVT-AFL injection. If no unambiguous allocation is possible because of missing parts of the AE start date for example, the AE will be treated as an AE (worst case scenario). [b]Ocular adverse events reported in ≥3 patients. There was 1 case of retinal artery occlusion. [c]All deaths were considered unrelated to IVT-AFL.

Conclusions

In AQUILA, the first study to assess the use of IVT-AFL in routine clinical practice in Latin America, **functional and anatomic outcomes of patients with DME improved over 12 months**

Despite not all patients receiving the recommended number of IVT-AFL injections for the treatment of DME, **mean BCVA improved by +8.1 letters in treatment-naïve patients and +4.6 letters in previously treated patients** over 12 months

No new safety signals were observed in AQUILA

AQUILA demonstrated that, in routine clinical practice, **patients treated regularly and intensely with IVT-AFL have the potential to achieve clinically relevant outcomes**

Thank you to all AQUILA patients and investigators

For more information, please contact:

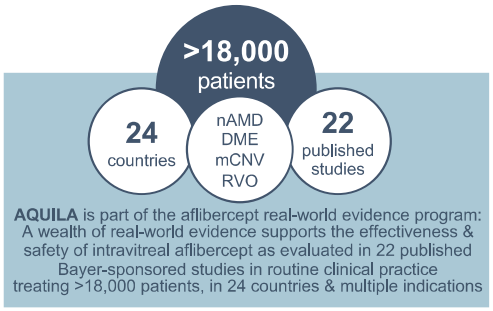
Prof. Francisco J. Rodriguez
fjrodriguez@fon.org.co

Disclosures

Francisco J. Rodriguez: Consultant: Bayer, Novartis, and Roche; Speaker: Bayer, Novartis, and Roche; Research funds: Novartis. **LW:** Speaker: Bayer and Quantel Medical; **AFB:** Speaker: Allergan, Bayer, and Novartis; **MC:** Consultant: Alcon; Speaker: Alcon, Bayer, and Novartis; Research funds: Alcon; **JKL, TM and MM:** Employees: Bayer AG, Berlin, Germany; **GG:** Employee: Bayer SA, Munro, Argentina; **JF-G**; Consultant: Bayer and Novartis; Speaker: Bayer, DORC, IOSA, and Novartis.

Acknowledgements

The AQUILA study was sponsored by Bayer AG, Berlin, Germany. Medical writing support, under the direction of the authors, was provided by ApotheCom and was funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidance (*Ann Intern Med* 2015;163:461–464).



Intravitreal aflibercept for the treatment of patients with neovascular age-related macular degeneration in routine clinical practice in Latin America: The AQUILA study

Lihteh Wu,[1] Arnaldo F. Bordon,[2] Martin Charles,[3] Francisco J. Rodriguez,[4] JinKyung Lee,[5] Tobias Machewitz,[5] Margarete Mueller,[5] Gabriela del Carmen Gay,[6] Jans Fromow-Guerra[7]

[1]Asociados de Macula, Vitreo y Retina de Costa Rica, San José, Costa Rica; [2]Hospital Oftalmológico de Sorocaba, Sorocaba, Brazil; [3]Centro Oftalmológico Dr Charles, Buenos Aires, Argentina; [4]Fundación Oftalmológica Nacional, Universidad del Rosario School of Medicine, Bogotá, Colombia; [5]Bayer AG, Berlin, Germany; [6]Bayer SA, Munro, Argentina; [7]Macula Retina Consultores, Mexico City, Mexico

Presented at European Society of Retina Specialists (EURETINA) Virtual Meeting, September 9–12, 2021

AQUILA (NCT03470103) study design

Purpose: To evaluate the clinical effectiveness (functional and anatomic outcomes) and safety of IVT-AFL in patients with nAMD or DME in routine clinical practice in Latin America

Patients: Aged ≥55 years with nAMD or aged ≥18 years with DME, treatment-naïve or previously treated

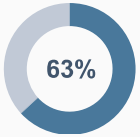
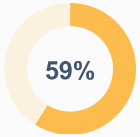
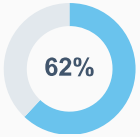
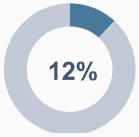
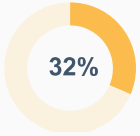
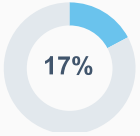
Treatment: IVT-AFL per routine clinical practice and following local prescribing recommendations

Primary endpoint: Mean change in BCVA from baseline to Month 12

[a]AQUILA DME data will be presented at EURETINA 2021 in the presentation titled "Intravitreal aflibercept for the treatment of patients with diabetic macular edema in routine clinical practice in Latin America: The AQUILA study".

BCVA, best-corrected visual acuity; **DME**, diabetic macular edema; **IVT-AFL**, intravitreal aflibercept; **nAMD**, neovascular age-related macular degeneration.

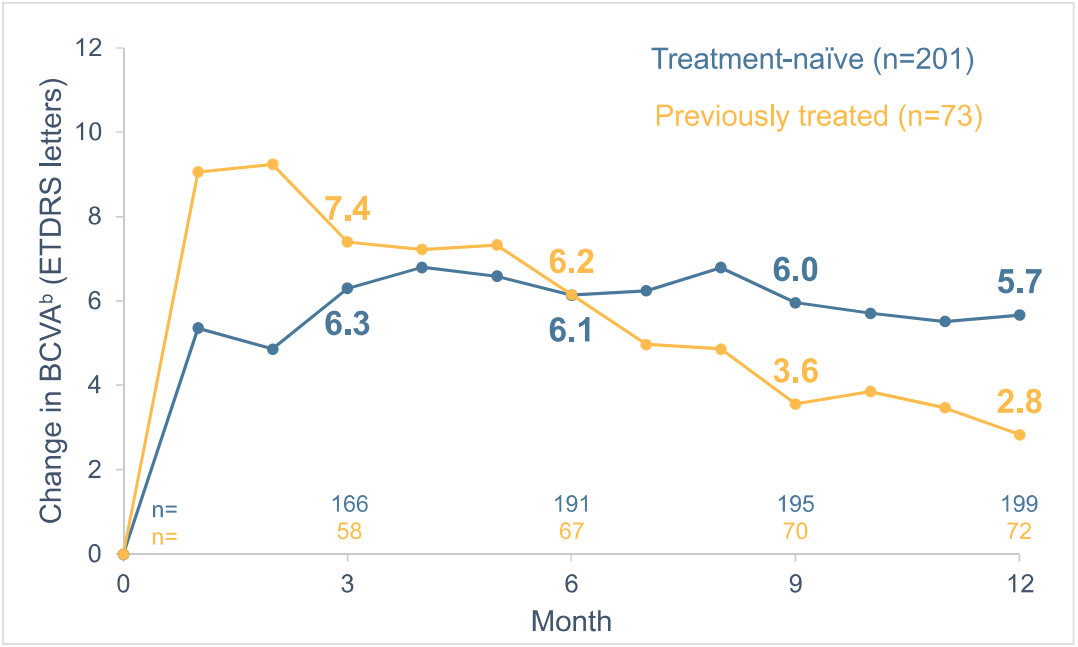
Baseline demographics, disease characteristics, and treatment exposure

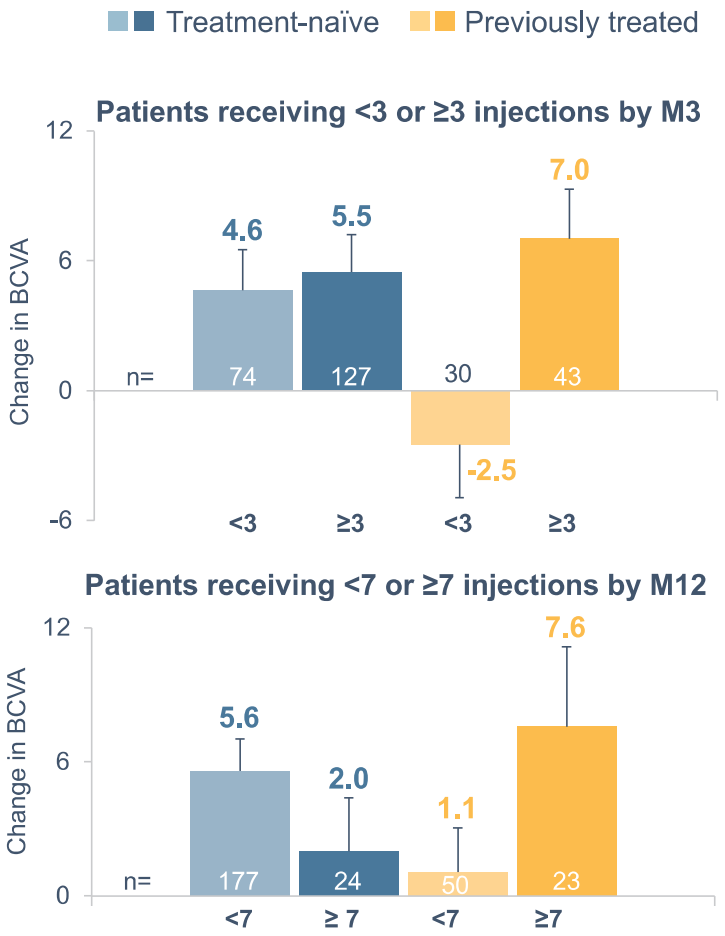
	Treatment-naïve nAMD (n=201)	Previously treated nAMD (n=73)	Overall population nAMD (N=274)
Age, years	**77.6** ±7.6	**76.1** ±8.3	**77.2** ±7.8
Female, n (%)	135 (**67**)	44 (**60**)	179 (**65**)
BCVA, ETDRS letters	**48.2** ±23.5	**47.7** ±21.4	**48.0** ±22.9
CRT, µm	**378** ±137	**400** ±137	**385** ±137
IVT-AFL injections			
By Month 6	**3.1** ±0.9	**3.6** ±1.3	**3.2** ±1.1
By Month 12	**4.2** ±1.9	**5.2** ±2.7	**4.4** ±2.2
≥3 within 3 months			
≥7 within 12 months			

Full analysis set; data are mean ±SD unless otherwise stated. Patient nationalities (FAS nAMD overall population): Argentina, n=196; Colombia, n=19; Costa Rica, n=18; Mexico, n=41.
CRT, central retinal thickness; **ETDRS,** Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set.

BCVA letter score over 12 months

By Month 12, mean BCVA improved: **+5.2** letters in treatment-naïve patients, and **+3.1** letters in previously treated patients[a]

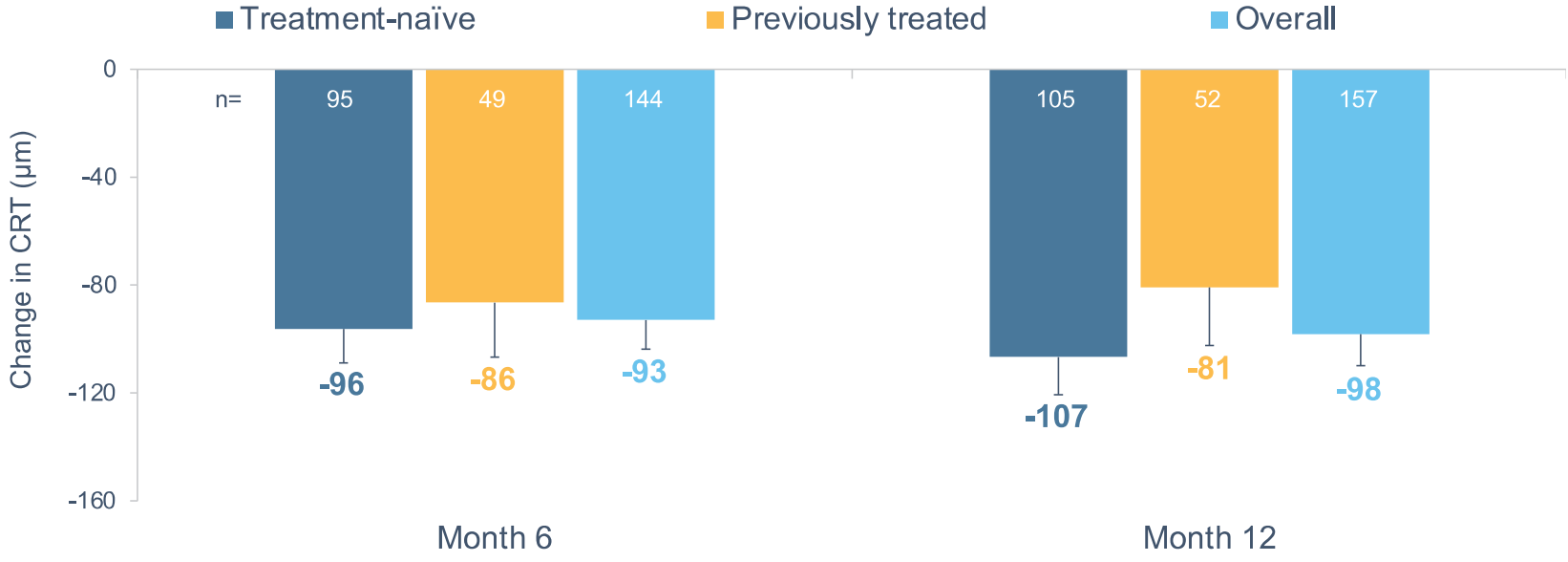




[a]Data were collected at 12 months ±60 days; mean BCVA improved from baseline to Month 12 by +5.2 ±18.3 and +3.1 ±15.3 letters. [b]Data were collected monthly ±15 days. FAS; missing data imputed using LOCF. Bar charts show mean ±SEM.

BL, baseline; **LOCF**, last observation carried forward; **M**, month; **SEM,** standard error of the mean.

Change in CRT at Month 6 and 12



The reduction in CRT at Month 12 was numerically greater in treatment-naïve patients

FAS; missing data imputed using LOCF. Data are mean ±SEM.

Safety summary[a]

Number of patients (%)	Overall population (N=324)
Any adverse event	24 (**7**)
Ocular adverse events[b]	18 (**6**)
Cataract	3 (**1**)
Conjunctival hemorrhage	3 (**1**)
Ocular serious adverse events	7 (**2**)
Ocular treatment-related adverse events	5 (**2**)
Non-ocular adverse events	6 (**2**)
Non-ocular serious adverse events	2 (**1**)
Non-ocular treatment-related adverse events	0
Deaths[c]	2 (**1**)

There were no cases of endophthalmitis, retinal vasculitis, or retinal artery occlusion

[a]Adverse events are those reported if they started after 1st IVT-AFL injection and not later than 30 days after last IVT-AFL injection. If no unambiguous allocation is possible because of missing parts of the AE start date for example, the AE will be treated as an AE (worst case scenario). [b]Ocular adverse events reported in ≥3 patients. There was 1 case of retinal artery occlusion. [c]All deaths were considered unrelated to IVT-AFL. Safety analysis set.

Conclusions

In AQUILA, the first study to assess the use of IVT-AFL in routine clinical practice in Latin America, **functional and anatomic outcomes of patients with DME improved over 12 months**

Despite many patients not receiving the recommended number of IVT-AFL injections, mean BCVA at 12 months improved by **+5.2 letters in treatment-naïve patients, and +3.1 letters in previously treated patients**

No new safety signals were observed in AQUILA; there were no cases of endophthalmitis, retinal vasculitis, or retinal artery occlusion

AQUILA demonstrated that, in routine clinical practice, patients treated **regularly and intensely with IVT-AFL have the potential to achieve clinically relevant outcomes**

Thank you to all AQUILA patients and investigators

For more information, please contact:

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Disclosures

Lihteh Wu: Speaker: Bayer and Quantel Medical. **AFB:** Speaker: Bayer, Allergan, and Novartis; **MC:** Consultant: Alcon; Speaker: Alcon, Bayer, and Novartis; Research funds: Alcon; **FJR:** Consultant: Bayer, Novartis, and Roche; Speaker: Bayer, Novartis, and Roche; Research funds: Novartis; **JKL:** Employee of Bayer AG, Berlin, Germany; **TM:** Employee of Bayer AG, Berlin, Germany; **MM:** Employee of Bayer AG, Berlin, Germany; **GG:** Employee of Bayer SA, Munro, Argentina; **JF-G:** Consultant: Bayer and Novartis; Speaker: Bayer, DORC, IOSA, and Novartis.

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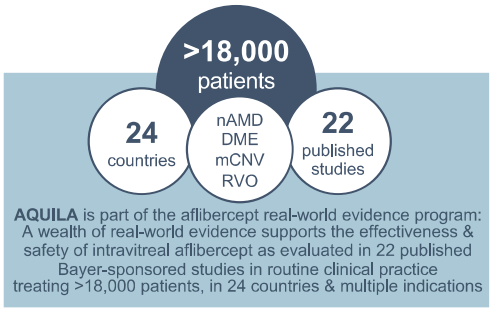

ANEXO No. 2

Cuadro resumen de publicaciones

INSTITUTO COSTARRICENSE DE INVESTIGACIONES CLINICAS

COMITÉ ETICO CIENTÌFICO CEC-ICIC

LISTADO DE PUBLICACIONES DE LOS ESTUDIOS APROBADOS SEGÚN LEY DE INVESTIGACION BIOMEDICA No. 9234

Enviado el 23-08-2021

No del Estudio	Nombre del Estudio		Título de la publicación	Nombre de los autores	Fecha de publicación	Datos de la Revista	Enlace de la publicación
CEC-ICIC-.E096-2018	AQUILA: Estudio observacional prospectivo en pacientes con degeneración macular húmeda relacionadaa la edad o edema macular diabético para evaluar la frecuencia de uso de aflibercept intravítreo, en la práctica clínica de rutina en América Latina	Dr. Lihteh Wu Tseng	Intravitreal aflibercept for the treatment of patients with diabetic macular edema in routine clinical practice in Latin America: The AQUILA study	Francisco J. Rodriguez,1 Lihteh Wu,2 Arnaldo F. Bordon,3 Martin Charles,4 JinKyung Lee,5 Tobias Machewitz,5 Margarete Mueller,5 Gabriela del Carmen Gay,6 Jans Fromow-Guerra7	September 9–12, 2021	Presented at European Society of Retina Specialists (EURETINA) Virtual Meeting.	PDF
			Intravitreal aflibercept for the treatment of patients with neovascular age-related macular degeneration in routine clinical practice in Latin America: The AQUILA study	Lihteh Wu,1 Arnaldo F. Bordon,2 Martin Charles,3 Francisco J. Rodriguez,4 JinKyung Lee,5 Tobias Machewitz,5 Margarete Mueller,5 Gabriela del Carmen Gay,6 Jans Fromow-Guerra7	September 9–12, 2021	Presented at European Society of Retina Specialists (EURETINA) Virtual Meeting.	PDF