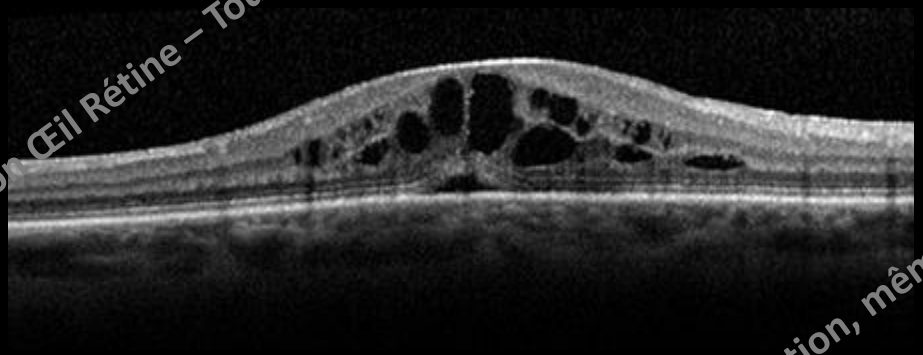
Anti-VEGF et OMD



Dr Fathalah BENBOUZID

Dr Vincent GUALINO

Centre Ophtalmologique Lyon Mermoz

LOR 8 & 9 DÉCEMBRE 2017 PALAIS DES CONGRÈS

CLINIQUE HONORÉ CAVE

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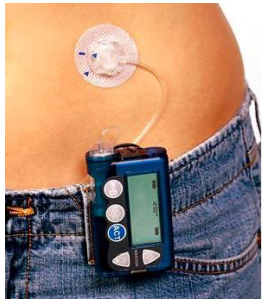
Traitement systémique de l'OMD



- **Glycémie**
  - **L'équilibre de l' HbA1C ne doit pas retarder le début du traitement**

- **HTA**: Nvlle norme **130/80** (AHA 11/2017) (insuffisance rénale, anémie..)

- **Dyslipidémies**
  - Hypercholestérolémie

Statines:
Macro circul
>
Micro circul

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group*

CONCLUSIONS

Intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive blood-pressure control, reduced the rate of progression of diabetic retinopathy. (Funded by the National Heart, Lung, and Blood Institute and others; ClinicalTrials.gov numbers, NCT00000620 for the ACCORD study and NCT00542178 for the ACCORD Eye study.)

  - Hypertriglycéridémie:

Fénofibrate
DNID
Réduction LK pour RD et non OMD

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

A C Keech, P Mitchell, P A Summanen, J O'Day, T M E Davis, M S Moffitt, M-R Taskinen, R J Simes, D Tse, E Williamson, A Merrifield, L T Laatikainen, M C d'Emden, D C Crimet, R L O'Connell, P G Colman, for the FIELD study investigators*

Interpretation Treatment with fenofibrate in individuals with type 2 diabetes mellitus reduces the need for laser treatment for diabetic retinopathy, although the mechanism of this effect does not seem to be related to plasma concentrations of lipids.

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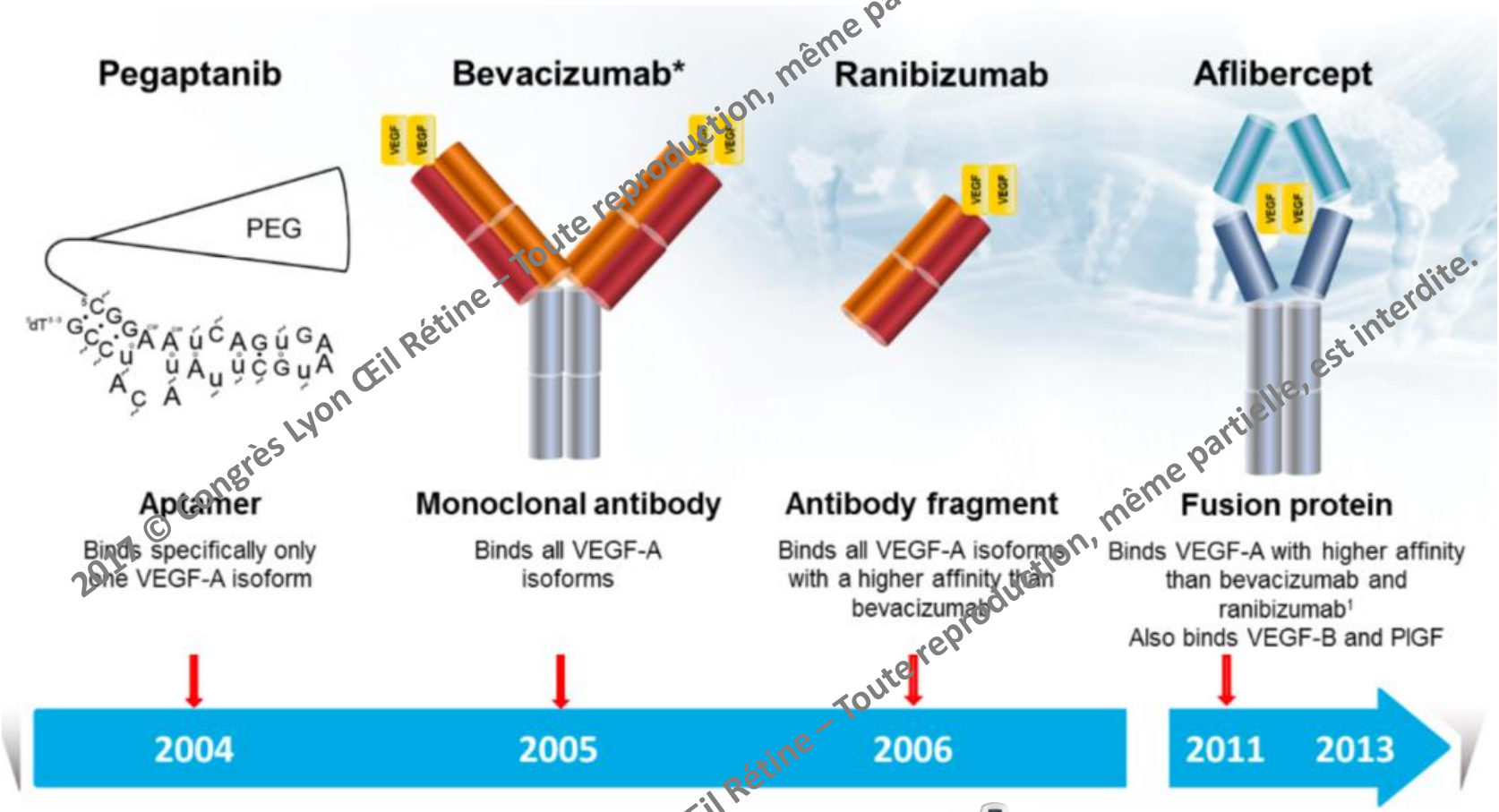
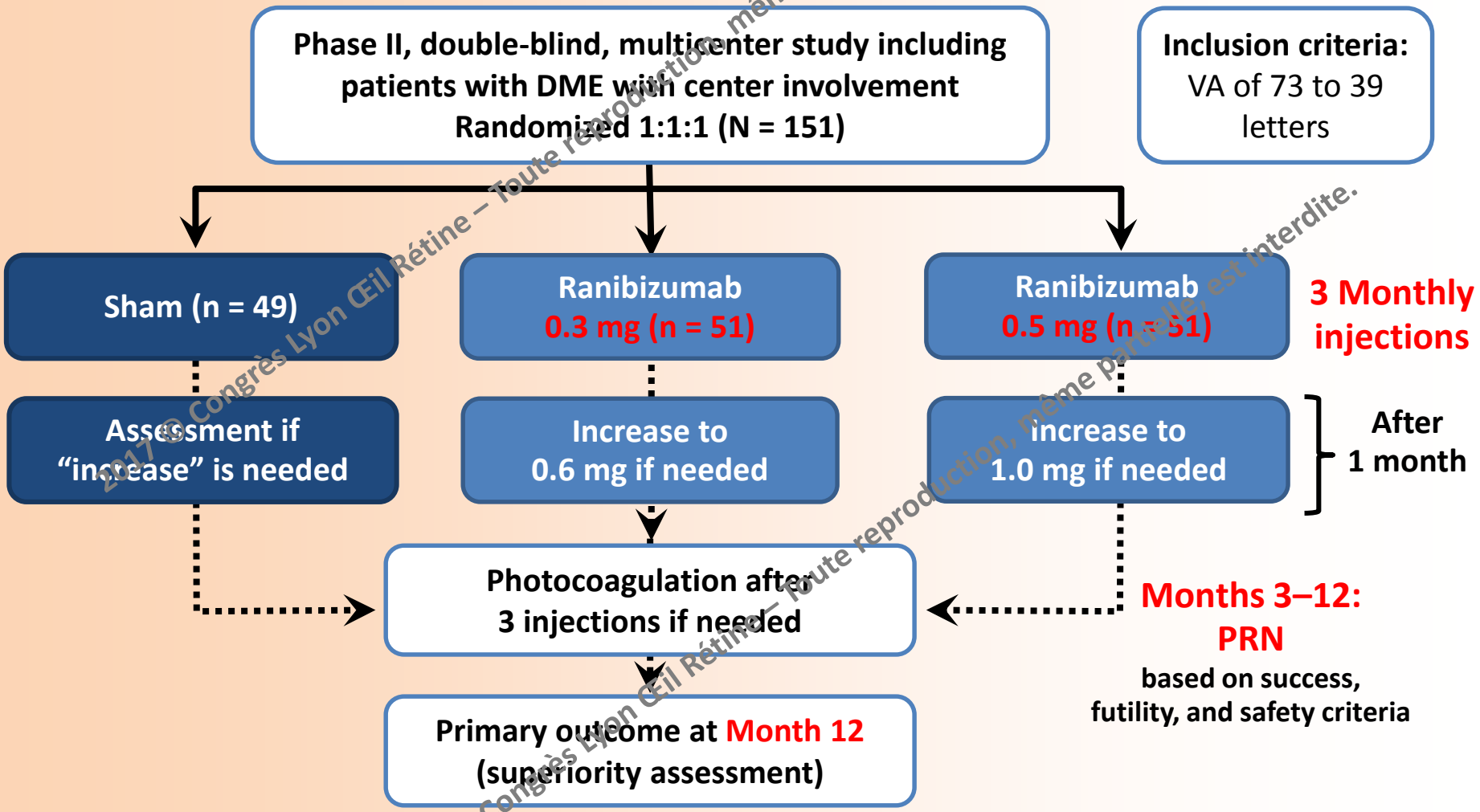
Les anti-VEGF en ophtalmologie

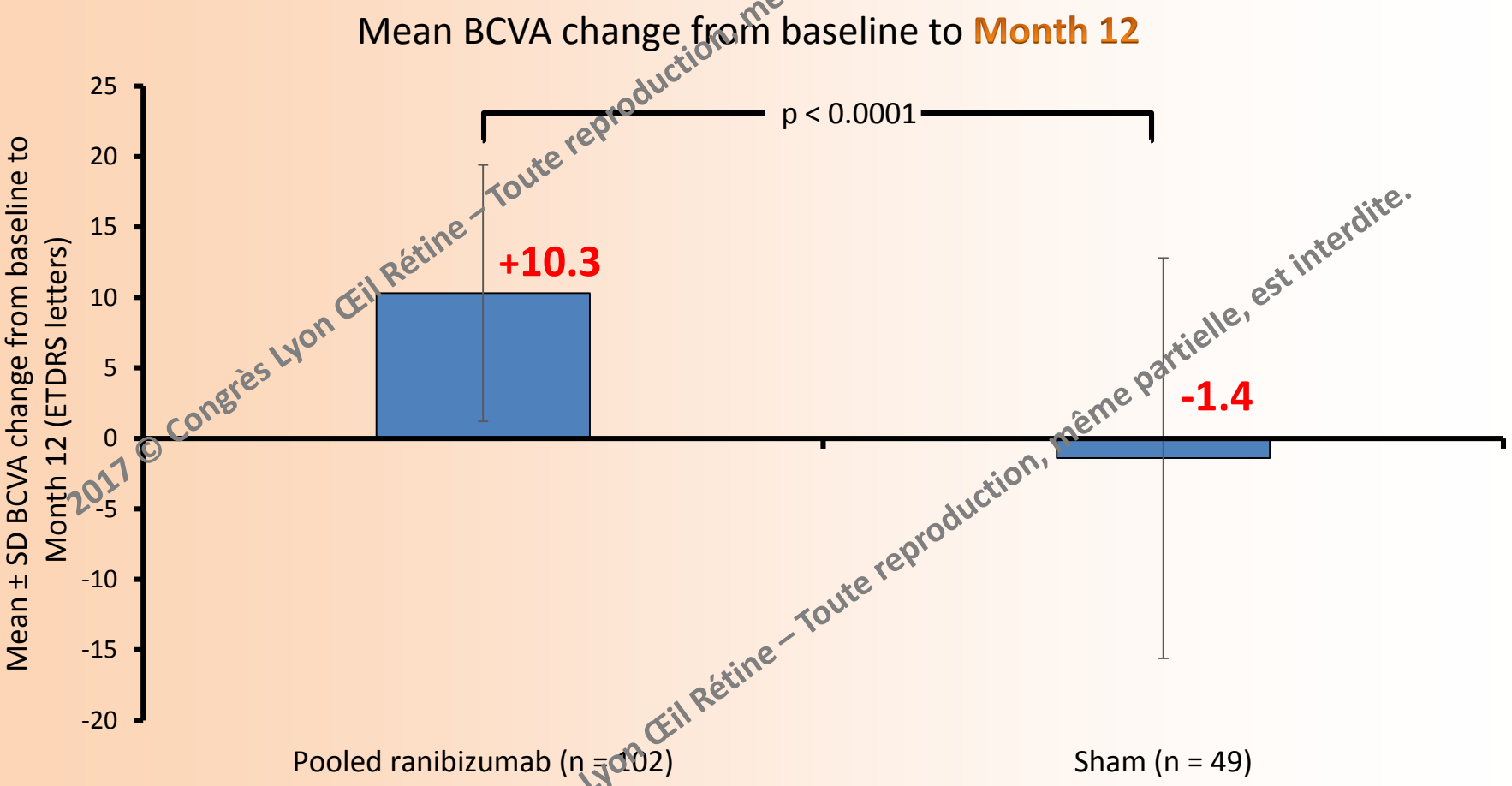


RESOLVE (2010): phase II, Ranibizumab Vs sham, 3+PRN,



Patients with center-involving DME in at least 1 eye (focal or diffuse) received 3 consecutive monthly RBZ 0.3 or 0.5 mg monthly injections, followed by an as-needed regimen with predefined retreatment criteria. Dose doubling and rescue laser were permitted at investigator discretion. DME, diabetic macular edema; PRN, *pro re nata*; VA, visual acuity
Massin P, et al. Diabetes Care 2010;33:2399-405

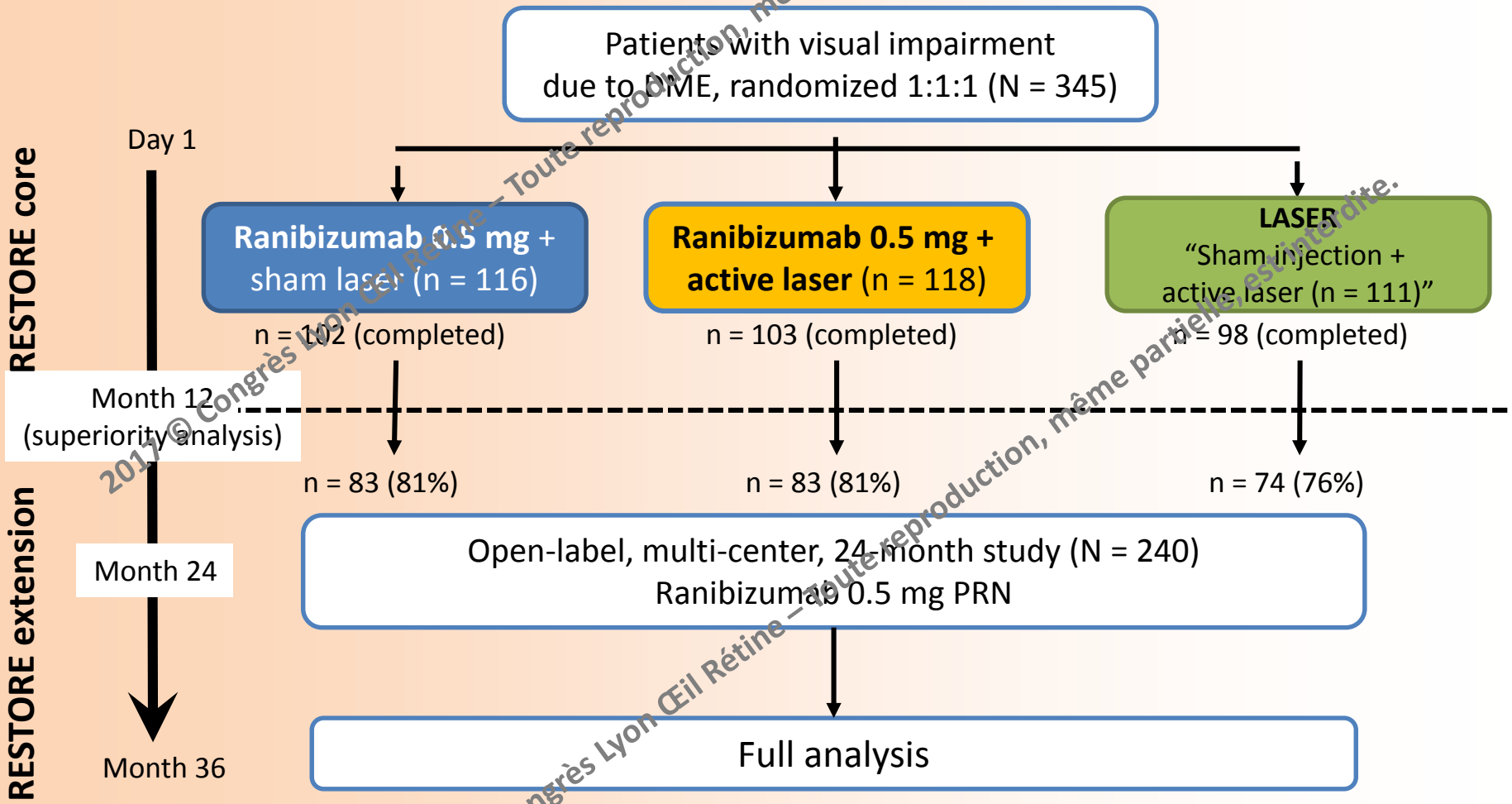
RESOLVE (2010): Ranibizumab > Sham in DME



Primary efficacy endpoint: mean average change from baseline to Month 1 through Month 12: Ranibizumab = 7.8 ± 7.7 ETDRS letters; Sham = -0.1 ± 9.8 ETDRS letters (p<0.0001)
Patients with center-involving DME in at least 1 eye (focal or diffuse) received 3 consecutive monthly RBZ 0.3 or 0.5 mg monthly injections, followed by an as-needed regimen with predefined retreatment criteria. Dose doubling and rescue laser were permitted at investigator discretion; BCVA, best-corrected visual acuity; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation
Massin, P, et al. Diabetes Care 2010;33:2399-405

RESTORE (2011 +2) :

Phase III, supériorité Ranibizumab Vs Laser, 3q4 puis PRN
efficacité au long terme et safety

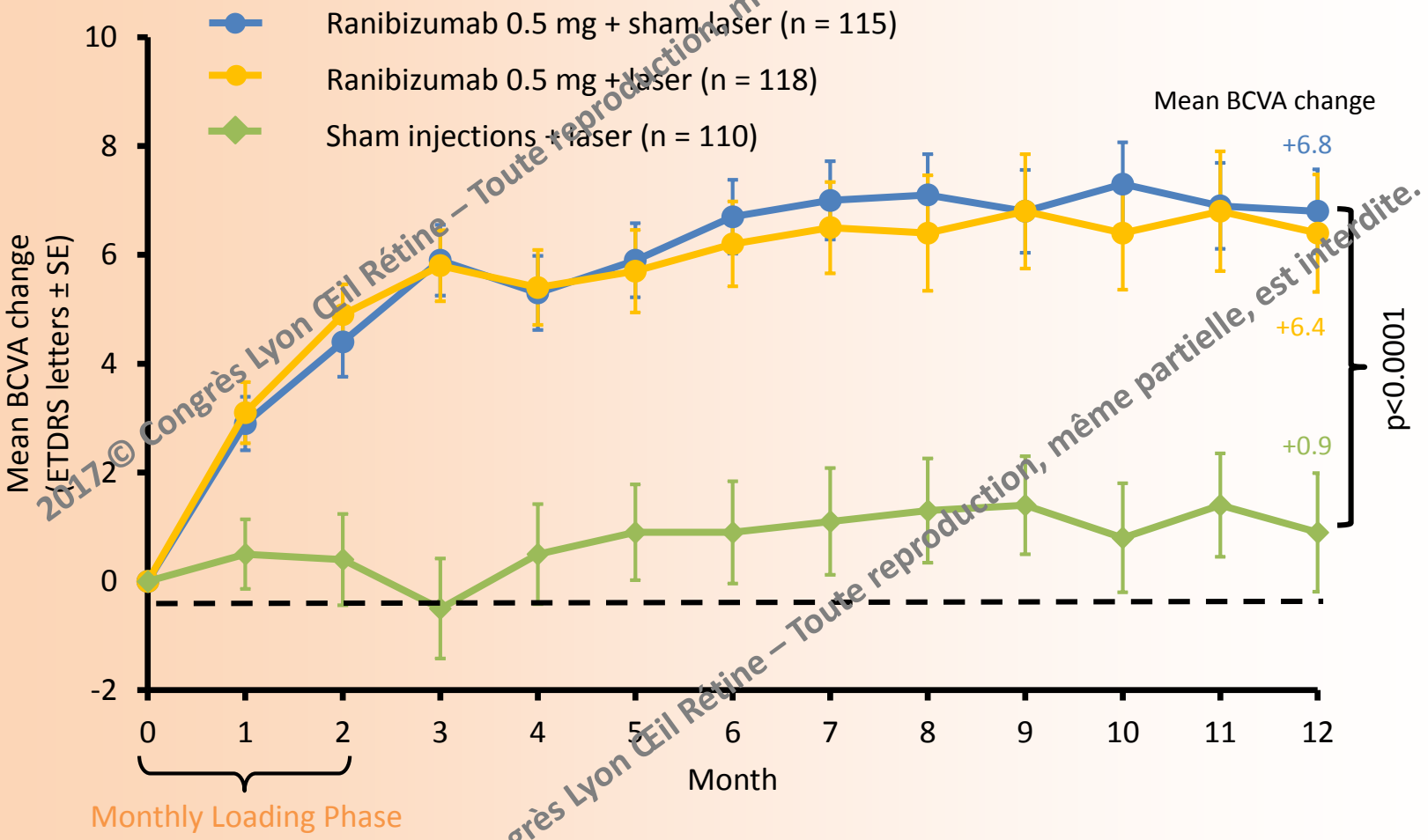


DME, diabetic macular edema; PRN, *pro re nata*

Schmidt-Erfurth U, et al. Ophthalmology 2014;121:1045-53

RESTORE (2010):

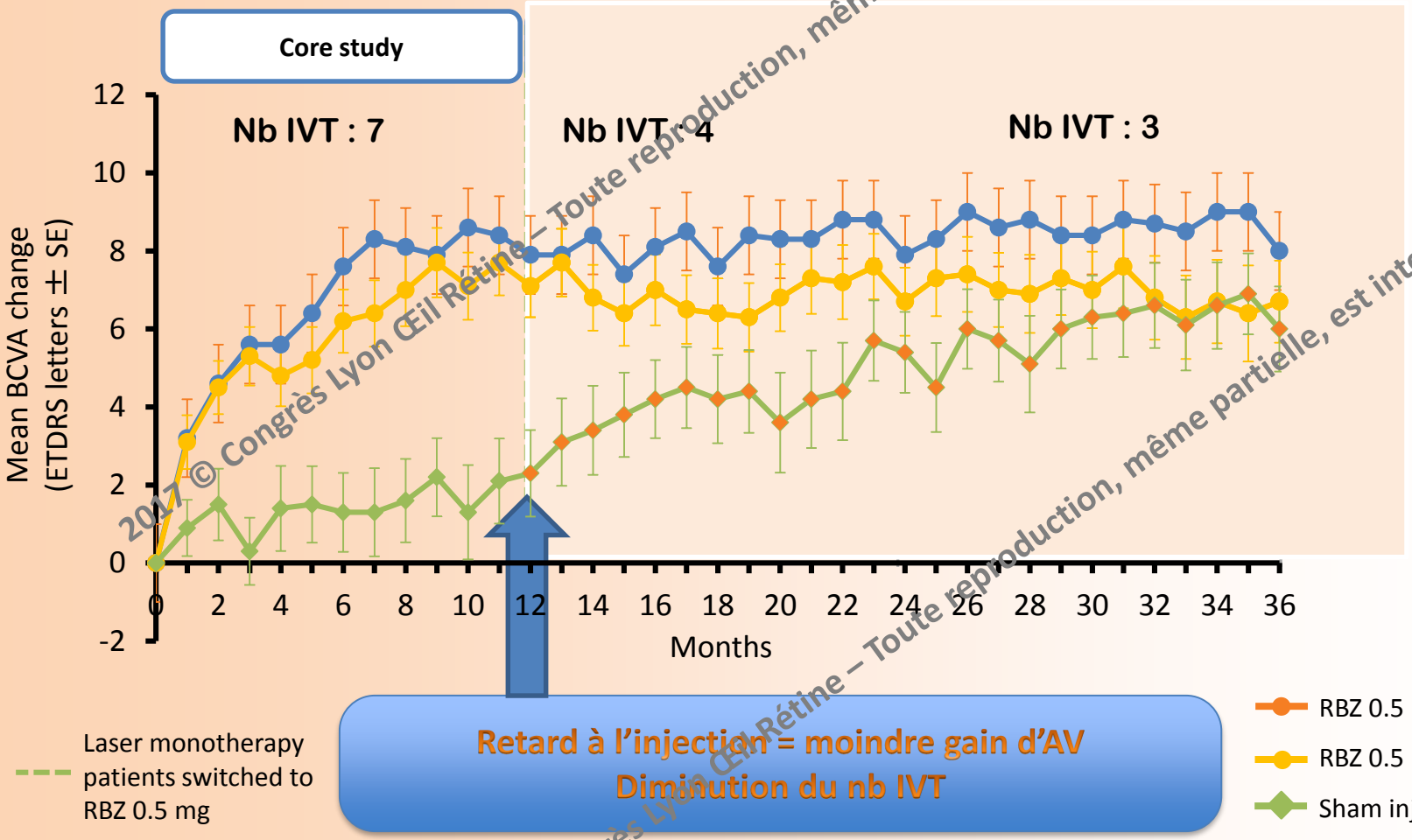
Ranibizumab « PRN » avec ou sans Laser > Laser seul (Gain d' AV)



Patients with center-involving DME received 3 consecutive monthly injections followed by other injections on a PRN basis and laser / sham laser was performed at baseline. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata*; SE, standard error

Mitchell P, et al. Ophthalmology 2011;118:615-25

RESTORE (2011+2):
Gain d'AV maintenu sur 36 mois (PRN)

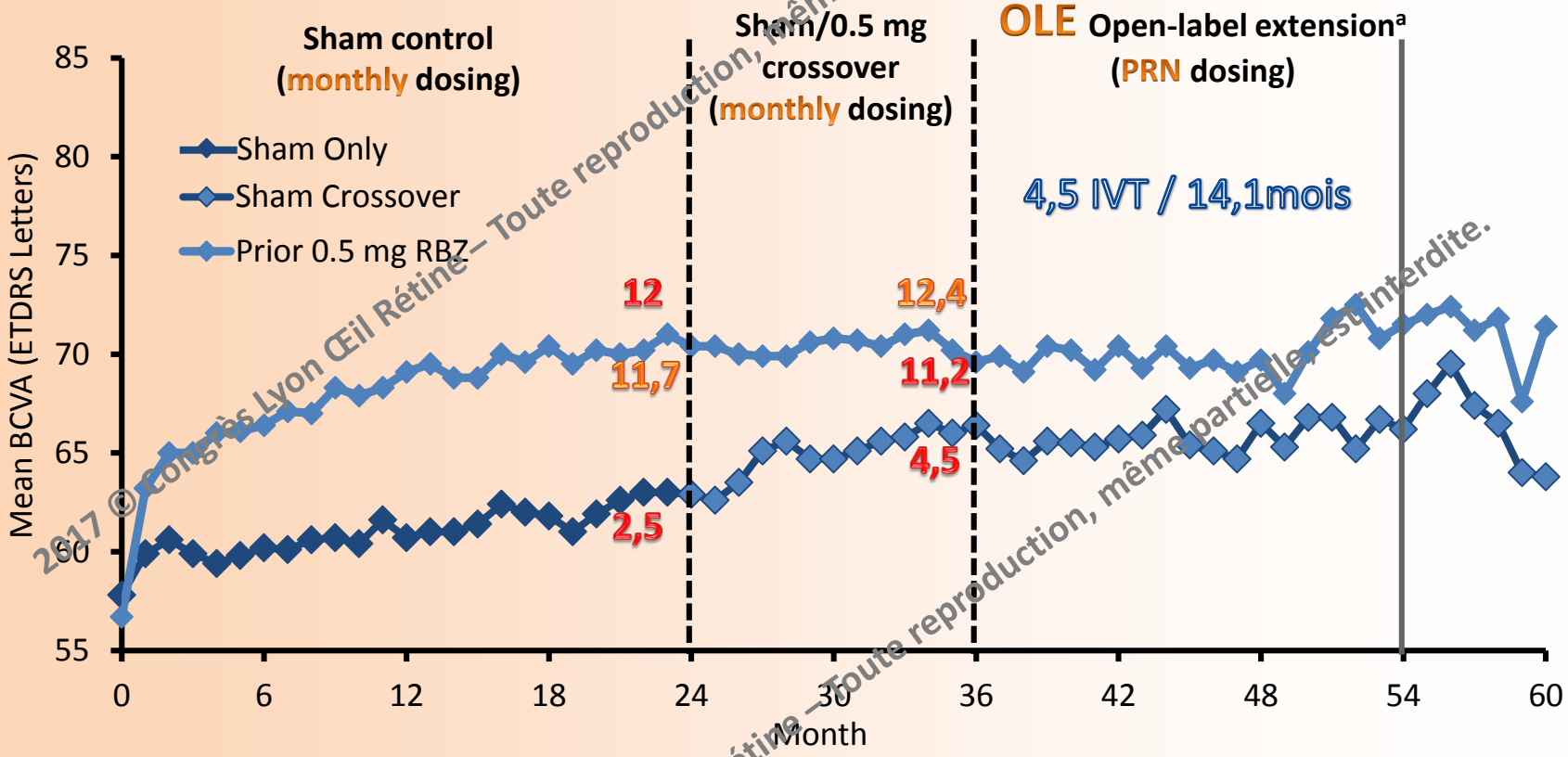


Patients received 3 consecutive monthly injections followed by other injections on a PRN basis and laser / sham laser was performed at baseline; active laser was performed PRN at investigator's discretion in accordance with ETDRS guidelines; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata;* RBZ, ranibizumab; SE, standard error; VA, visual acuity

Schmidt-Erfurth U, et al. Ophthalmology 2014;121:1045-53

RISE / RIDE /OLE :

Ranibizumab mensuel puis PRN



Gain d'AV stable à 36 mois régime Mensuel

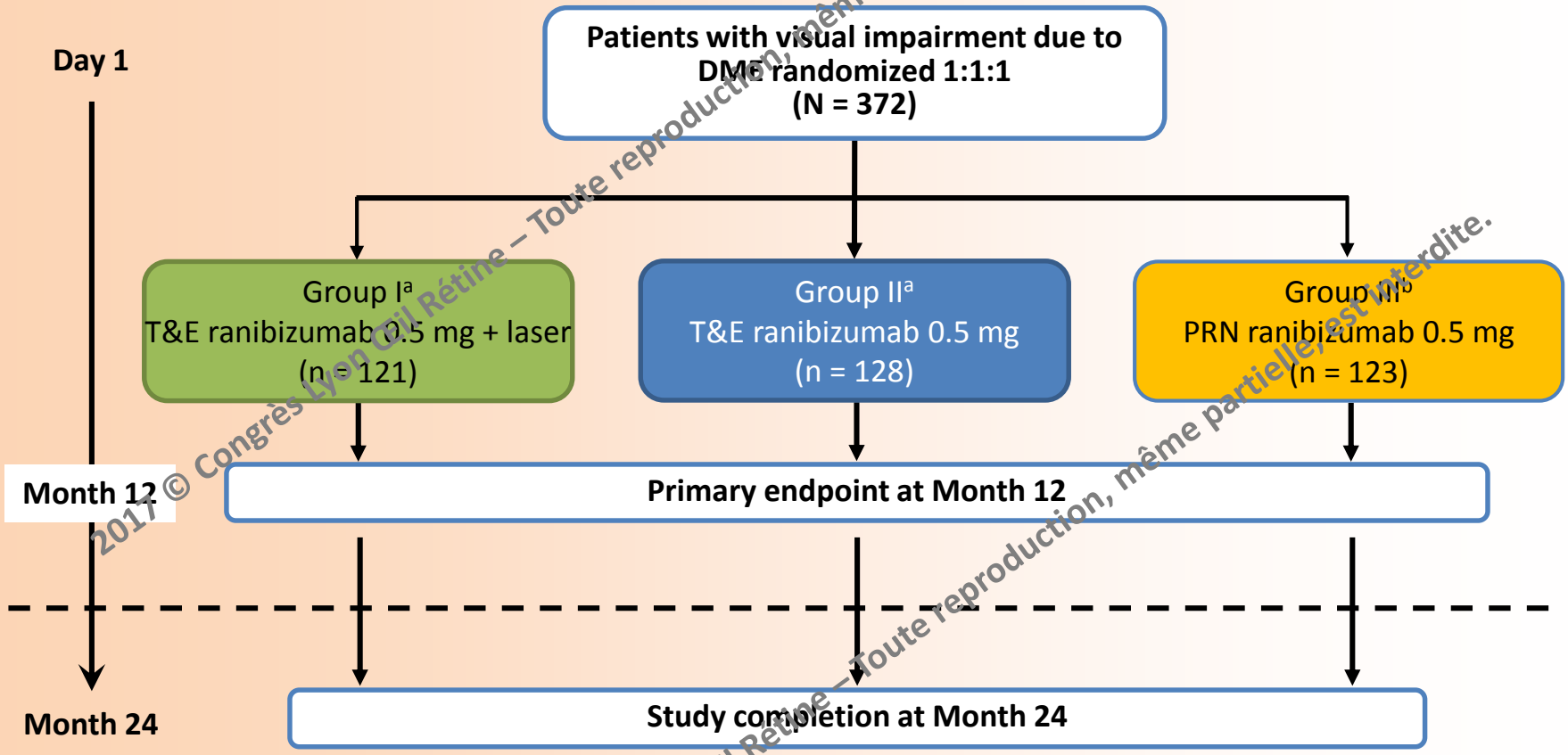
PRN Gain d'Av maintenu et réduction nb IVT (4,5 IVT en 14,1mois)

IVT précoces = gain AV supérieur

[a]Data become unstable after Month 54 due to the low number of patients at that point. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata;* RBZ, ranibizumab; VA, visual acuity

Morse L, et al. 37th Annual Meeting of the Macula Society. February 19-22, 2014. Key Largo, FL, USA

RETAIN: T&E (+/- Laser) Vs PRN



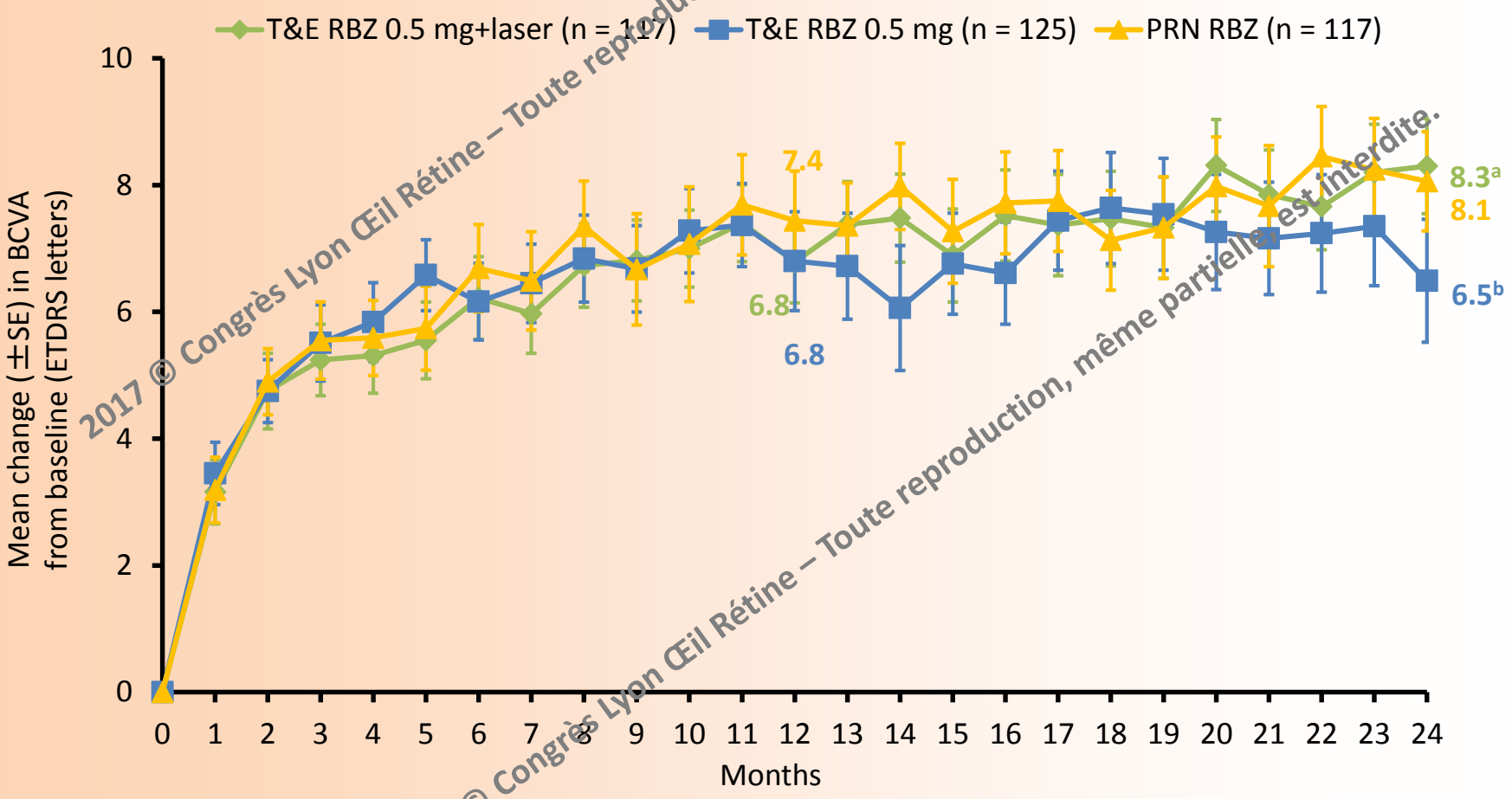
[a]Group I/II: Ranibizumab injection at baseline (Group I: additional laser treatment at baseline and PRN subsequently according to ETDRS guidelines); monthly ranibizumab 0.5 mg treatment until VA stability, monthly monitoring, incremental extension in the inter-treatment interval by 1 month (maximum prolongation up to 3 months) at stable VA, when VA decreases due to DME at T&E visit resume monthly treatment until VA stability and re-enter the extension treatment phase; [b]Group III: Ranibizumab injection at baseline, monthly treatment until VA stability, monthly monitoring, when VA decreases due to DME resume monthly treatment until VA stability; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata*; T&E, treat and extend; VA, visual acuity

Prünte C, et al. AAO Annual Meeting Retina Subspecialty Day. Nov 15, 2013. New Orleans, LA, USA

RETAIN:

Gain AV maintenu en T&E

Pas de différence statistiquement significative entre les trois bras à M12 et M24



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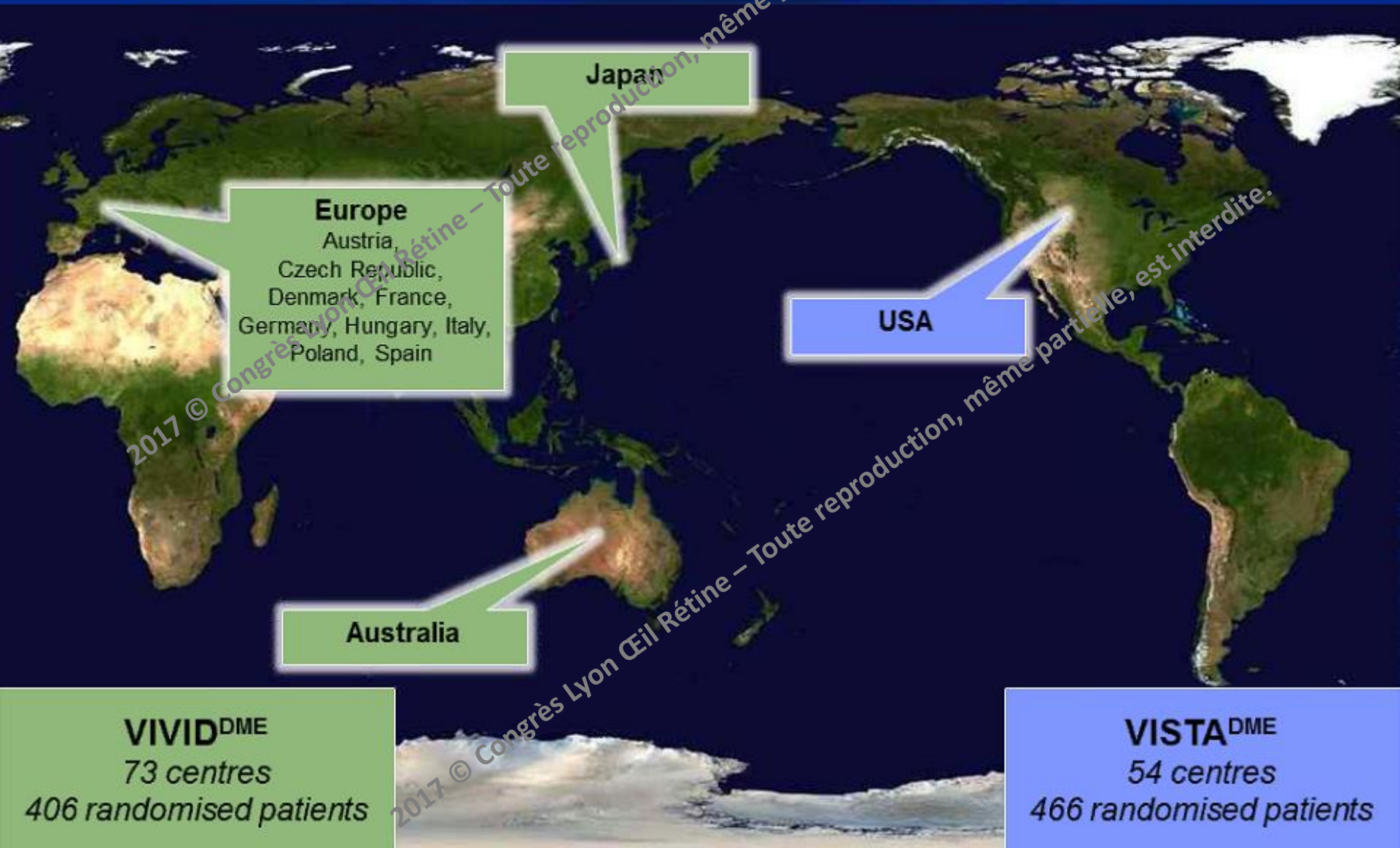
[a]p = 0.9327 vs PRN; [b]p = 0.1599 vs PRN; CMH test (row mean scores statistic) with the observed values as scores; Full analysis set (MV/LOCF, mean value interpolation/last observation carried forward); CMH, Cochran-Mantel-Haenszel; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata*; RBZ, ranibizumab; T&E, treat and extend

Prünte C, et al. AAO Annual Meeting Retina Subspecialty Day. Nov 15, 2013. New Orleans, LA, USA

Study Sites



VIVID^{DME}
73 centres
406 randomised patients

VISTA^{DME}
54 centres
466 randomised patients

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Study Design

Patients with clinically significant DME

with central involvement and ETDRS BCVA 20/40 to 20/320

N=406 (VIVID^{DME}) N=466 (VISTA^{DME})

Patients randomised 1:1:1

- **IVT-AFL 2 mg q4 wks†**
- **IVT-AFL 2 mg q8 wks*,†**
- **Laser photocoagulation†,‡**

Primary endpoint: Week 52

Critère principal
Variation moyenne MAVC par rapport à la baseline

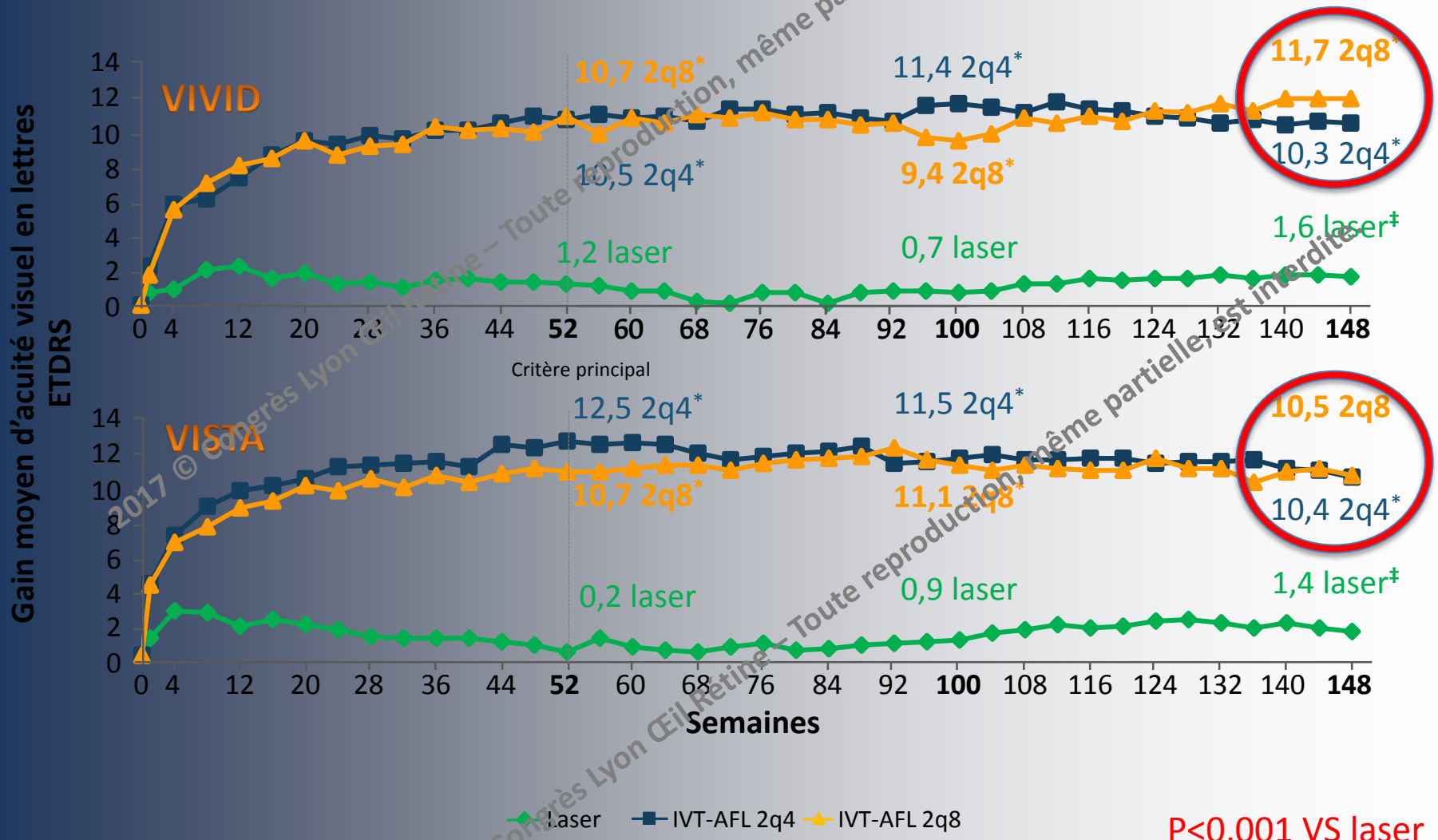
Critères secondaires
% Gain MAVC ≥15 lettres
Delta ≥2 Score DRSS
Delta CRT

Continued treatment through Year 3

*After 5 initial monthly doses; †at Week 24 additional active treatment was allowed in the case of disease reoccurrence/worsening based on prespecified criteria (laser in the IVT-AFL arms/IVT-AFL in the laser arm); ‡at Year 3 IVT-AFL could be given as needed if retreatment criteria met.
BCVA, best-corrected visual acuity; DME, diabetic macular edema; DRSS, diabetic retinopathy severity score; IVT-AFL, intravitreal aflibercept.

VIVID/VISTA:

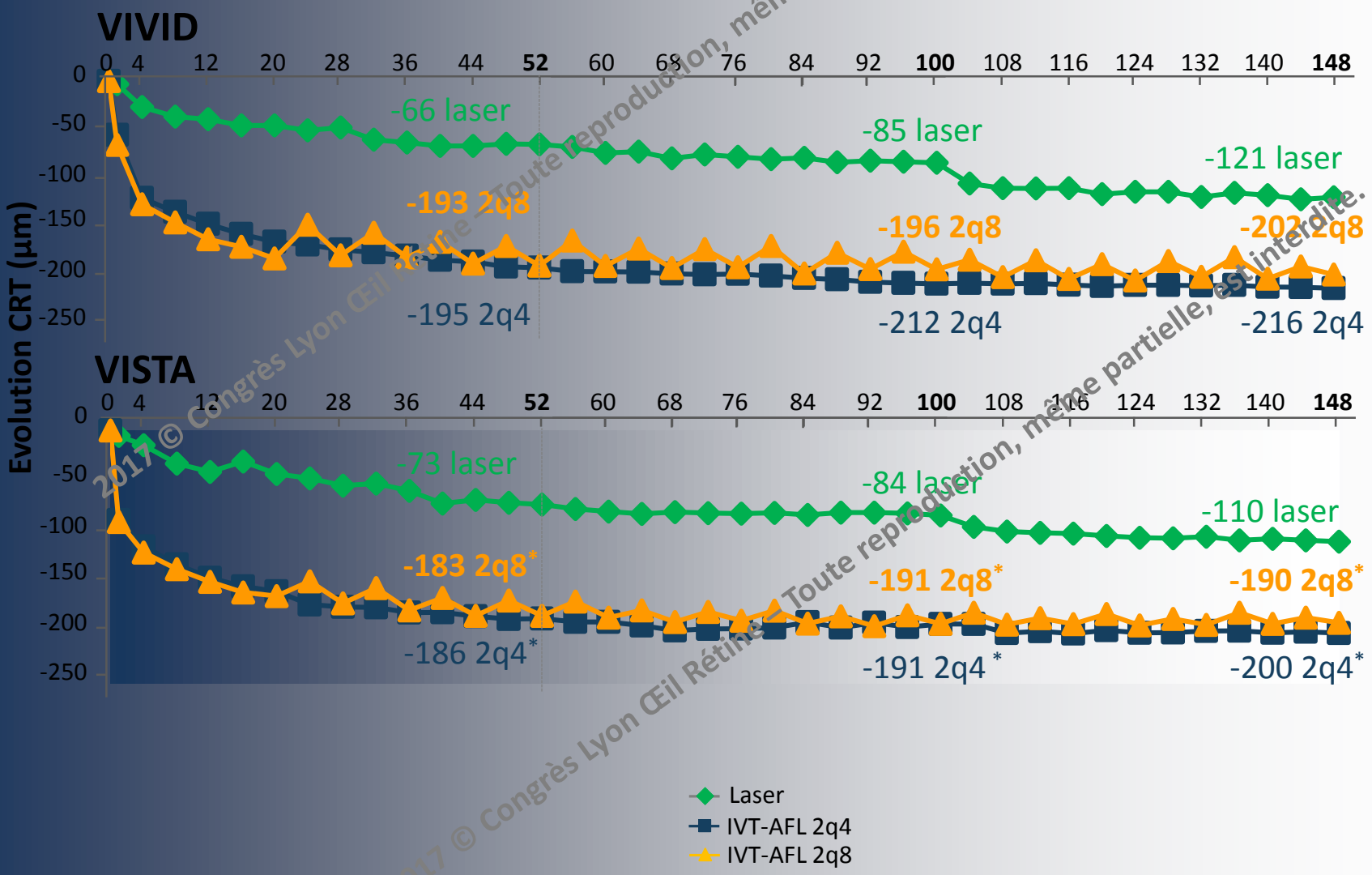
Gain AV



P<0,001 VS laser

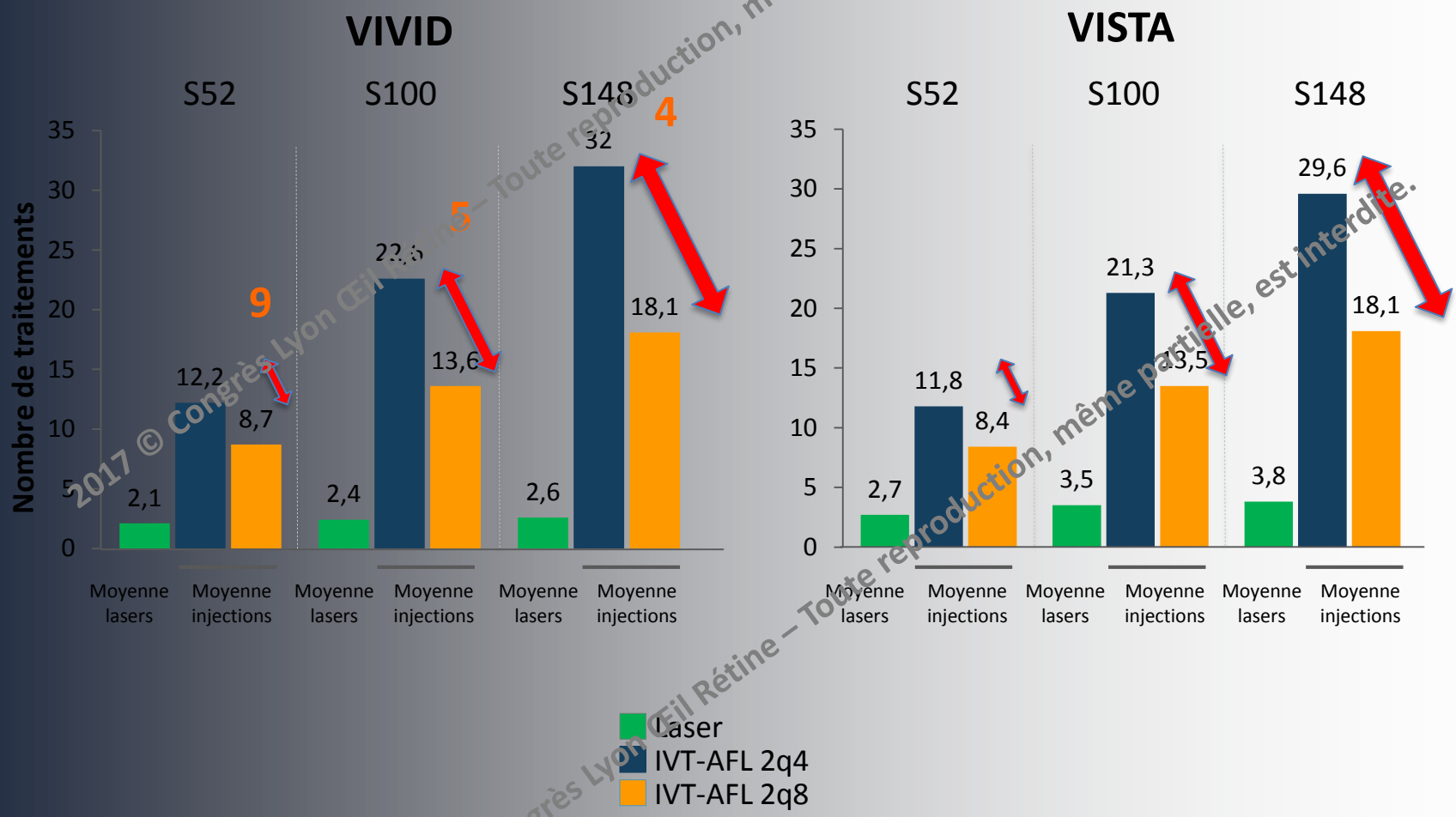
VIVID/VISTA:

Evolution CRT (OCT)



VIVID/VISTA:

Nombre IVT en diminution (2q4 / 2q8)



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Korobelnik J-F, et al. Ophthalmology. 2014 Nov;121(11):2247-54

Conclusions VIVID & VISTA

Critère principal
Variation moy MAVC / baseline

- Amélioration de la MACV Aflibercept > Laser
- Gain moyen de 12 lettres , 40% gain 3 lignes ETDRS

Critères secondaires
% Gain MAVC ≥15 lettres
Delta ≥2 Score DRSS
Delta CRT

- Amélioration anatomique OCT (CRT) rapide et stable dans le temps
- Équivalence Aflibercept 2q8 et Aflibercept 2q4 (MAVC et OCT)
- Réduction de 2 stades DRSS pour 40% des patients
- Bonne tolérance et sécurité du traitement

=> Schéma Aflibercept 2q8 proactif : réduit le nb IVT, nb visites => AMM

Résultats concluants ?
Oui, Mais…

Endurance phase IV ouverte PRN

Outcomes With As-Needed Aflibercept and Macular Laser Following the Phase III VISTA DME Trial: ENDURANCE 12-Month Extension Study

CHARLES C. WYKOFF, RYAN T. LE, RAHUL N. KHURANA, DAVID M. BROWN, WILLIAM C. OU, RUI WANG, W. LLOYD CLARK, AND DAVID S. BOYER, ON BEHALF OF THE ENDURANCE STUDY GROUP

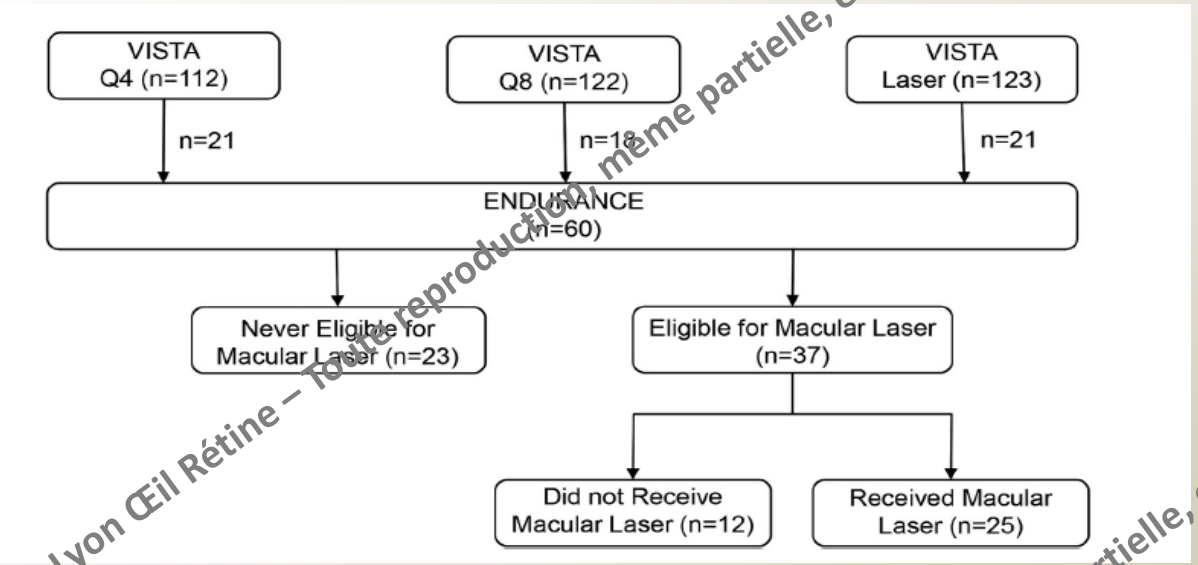
Am J Ophthalmol. 2017 Jan;173:56-63

Long-term outcomes with as-needed aflibercept in diabetic macular oedema: 2-year outcomes of the ENDURANCE extension study

Charles C Wykoff,[1,2] William C Ou,[1] Rahul N Khurana,[3,4] David M Brown,[1,2] W Lloyd Clark,[5] David S Boyer,[6] for the ENDURANCE Study Group

Br J Ophthalmol. 2017 Aug 16

Protocole de l'étude



- **60 patients** issus de VISTA
- **Traitement** PRN
- **Suivi:** 4s « si pas IVT 3 visites » -> 8s « si pas IVT 3 visites » -> 12s

OMD -> IVT

- **Laser :** Si >2 IVT pendant les 24s **Re-LASER** à 90 jours si encore 2IVT

- **Critères d'évaluation :**

- **Principal : Nb IVT à 12 mois / 24 mois**
- **Secondaires : évolution MAVC et CRT**

Résultats 12M (4 ème année)

Principal:

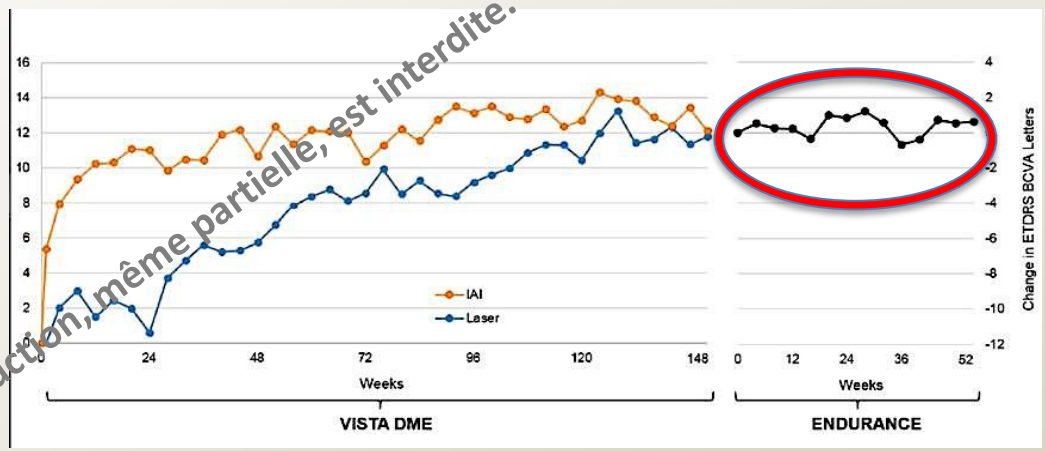
- 30% stables sans IVT
- 4,5 IVT en moyenne 12 mois
- 62% laser sans de réduction nb IVT

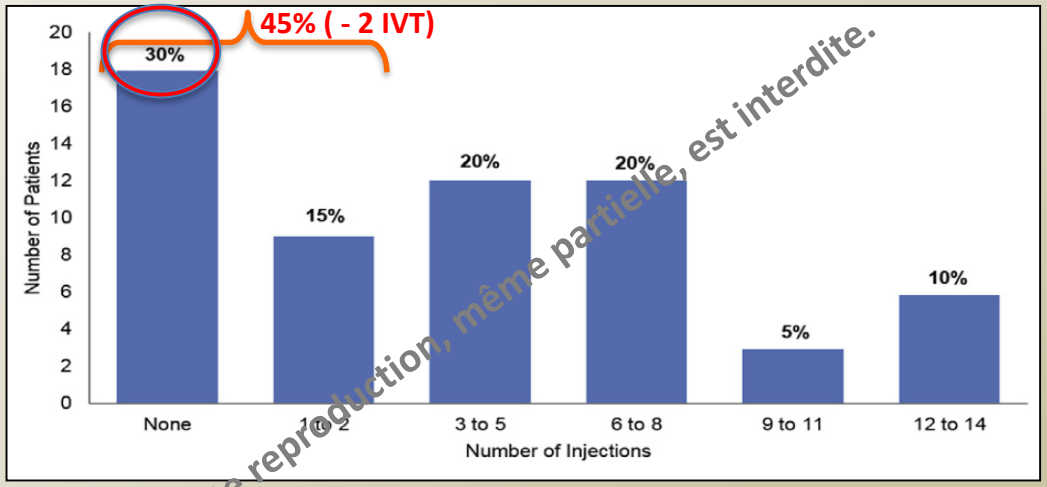
Secondaires

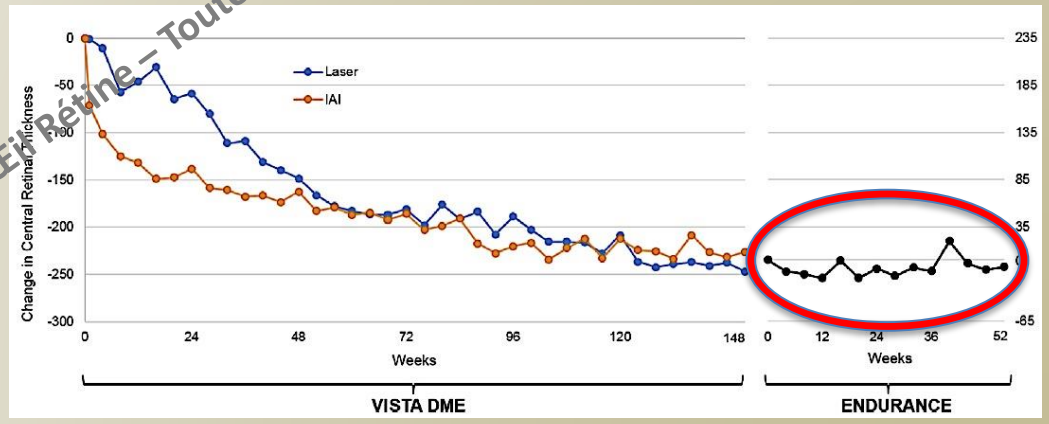
- Gain AV stabilisé (+/- 1,5 Lettre)
- Assèchement OCT stabilisé
- Evo DRSS (2 patients RDNP-> RDP)
- Tolérance : RAS

OLE Study (RISE / RIDE) : Ranibizumab
24.2% patients sans IVT
4,5 IVT en moyenne 14,1 mois

Plus de tolérance micro récidives OMD?







Résultats 24 M (5 ème année)

Principal:

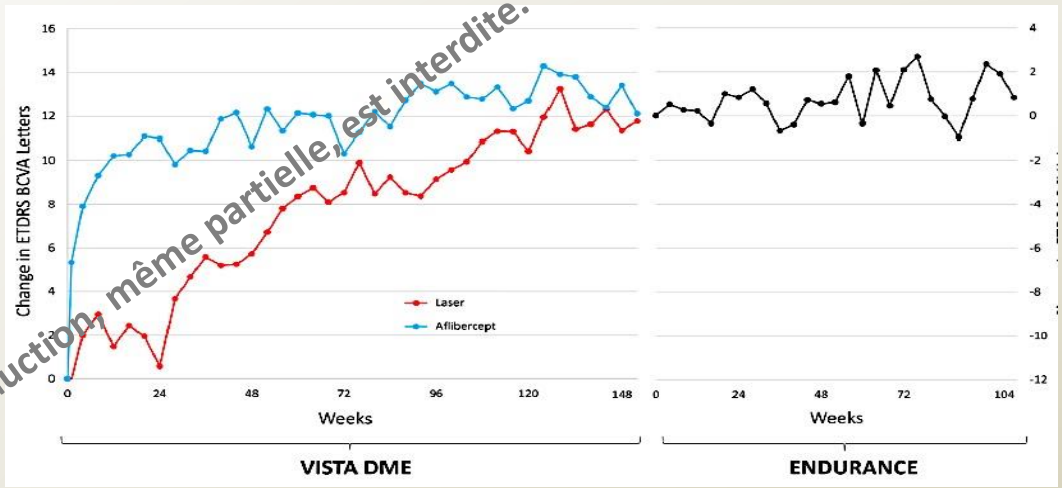
- 25 % sans IVT (0-24 M)
- 7,7 IVT en moyenne (0-24 M)
  - 4,5 IVT en moyenne 0-12 M
  - 3,4 IVT en moyenne 12-24 M

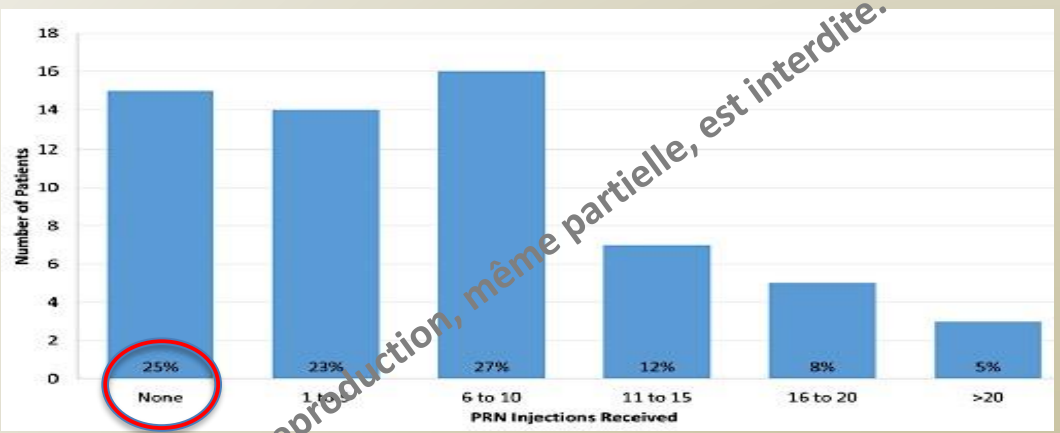
- 45% laser (0-24)
  - 26% laser (12-24M)

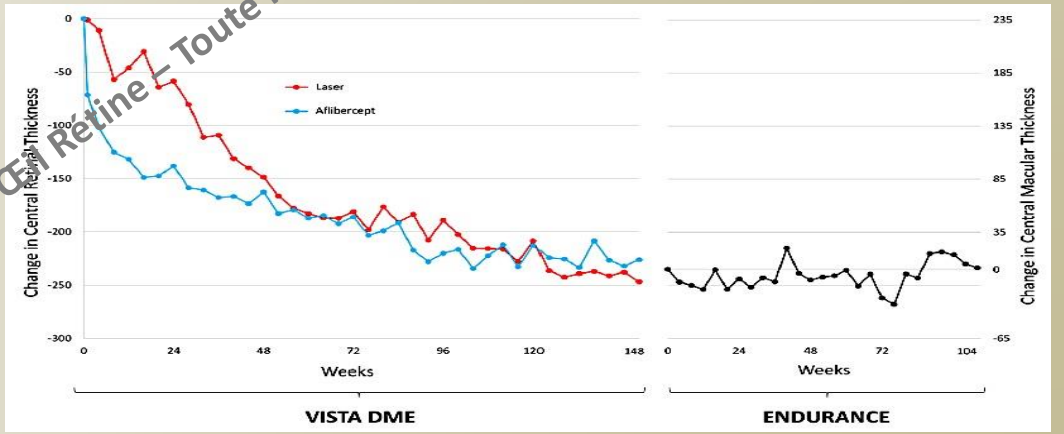
    - Pas de réduction IVT
    - Pas d'impact CRT
    - Pas d'impact MAVC

Secondaires:

- Gain AV stabilisé (+/- 3 Lettres / VISTA)
- Assèchement OCT stabilisé
- Evo DRSS : 10% RDNP-> RDP
- Pas de lien nb IVT / Evo RDP (p=0,10)
- Tolérance : RAS







Quelle molécule ?

Le choix peut être difficile mais y réfléchir n'est pas inutile…

DRCR.net (Protocole T)

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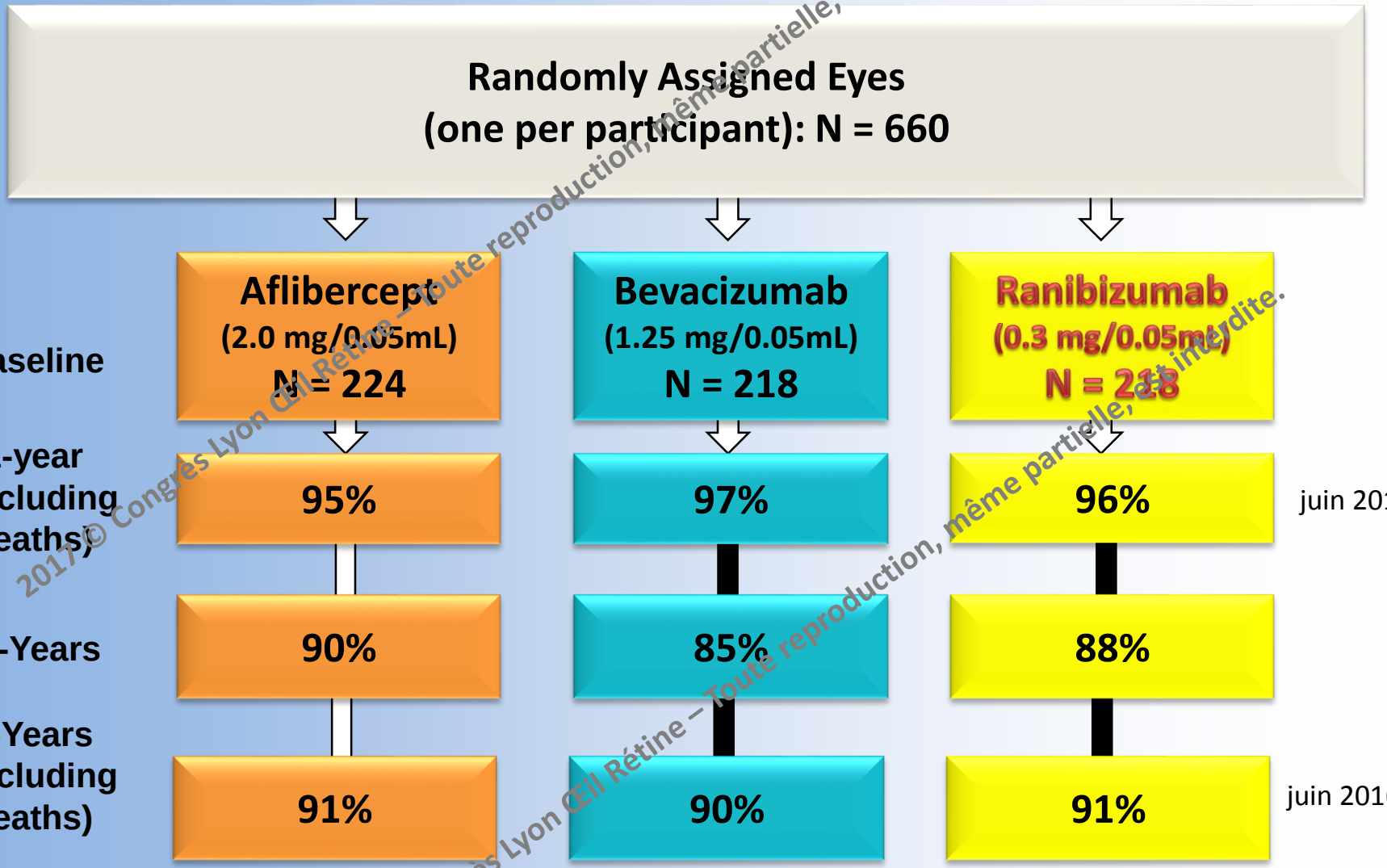
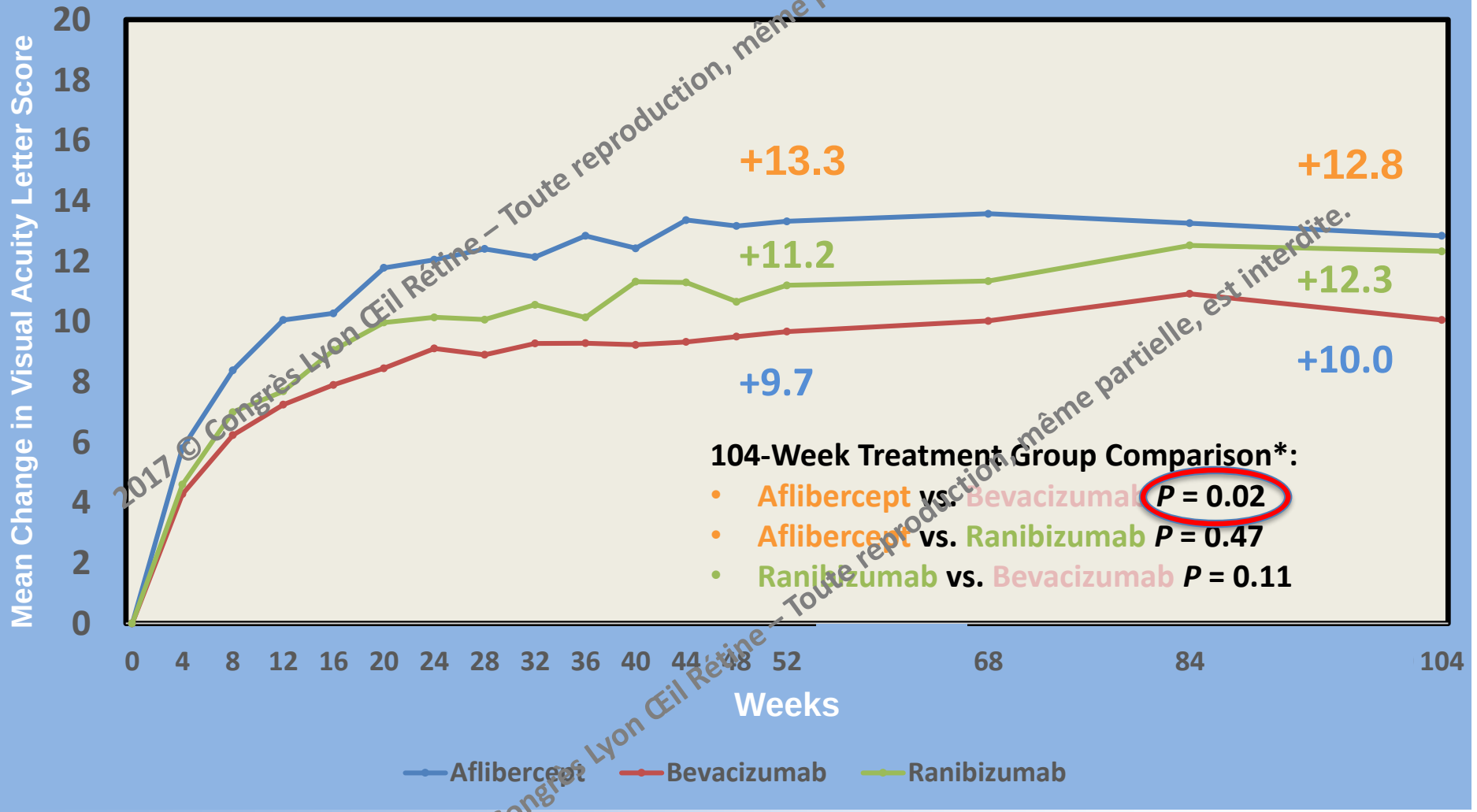
Protocole T: Randomization



Mean Change in Visual Acuity Over 2 Years

Full Cohort



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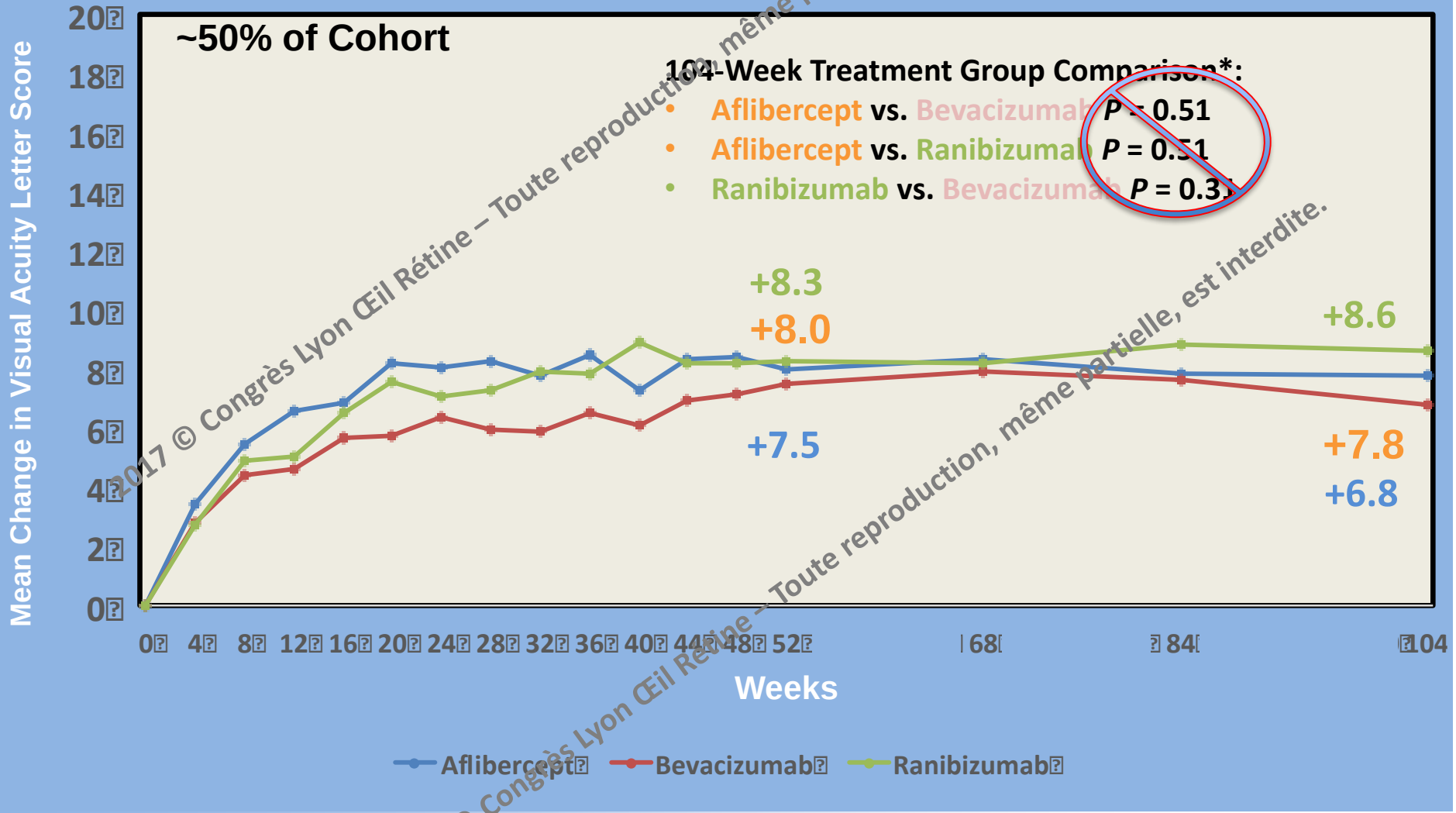
* *P*-values adjusted for baseline visual acuity and multiple comparisons

Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity ***20/32 to 20/40***



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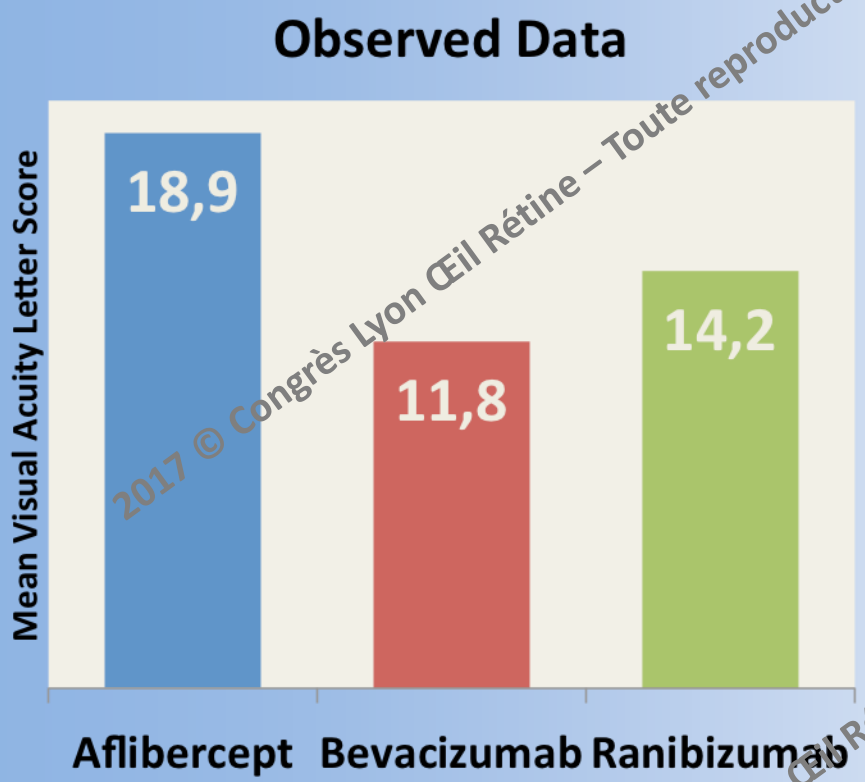
* *P*-values adjusted for baseline visual acuity and multiple comparisons

Visual Acuity Outcomes

Baseline = 20/50 or Worse



Treatment Group Comparisons

	Difference	CI	*P*-Value
Aflibercept vs Bevacizumab	+6.5	+2.9 to +10.1	<0.001
Aflibercept vs Ranibizumab	+4.7	+1.4 to +8.0	0.0031
Ranibizumab vs Bevacizumab	+1.8	-1.1 to +4.8	0.21

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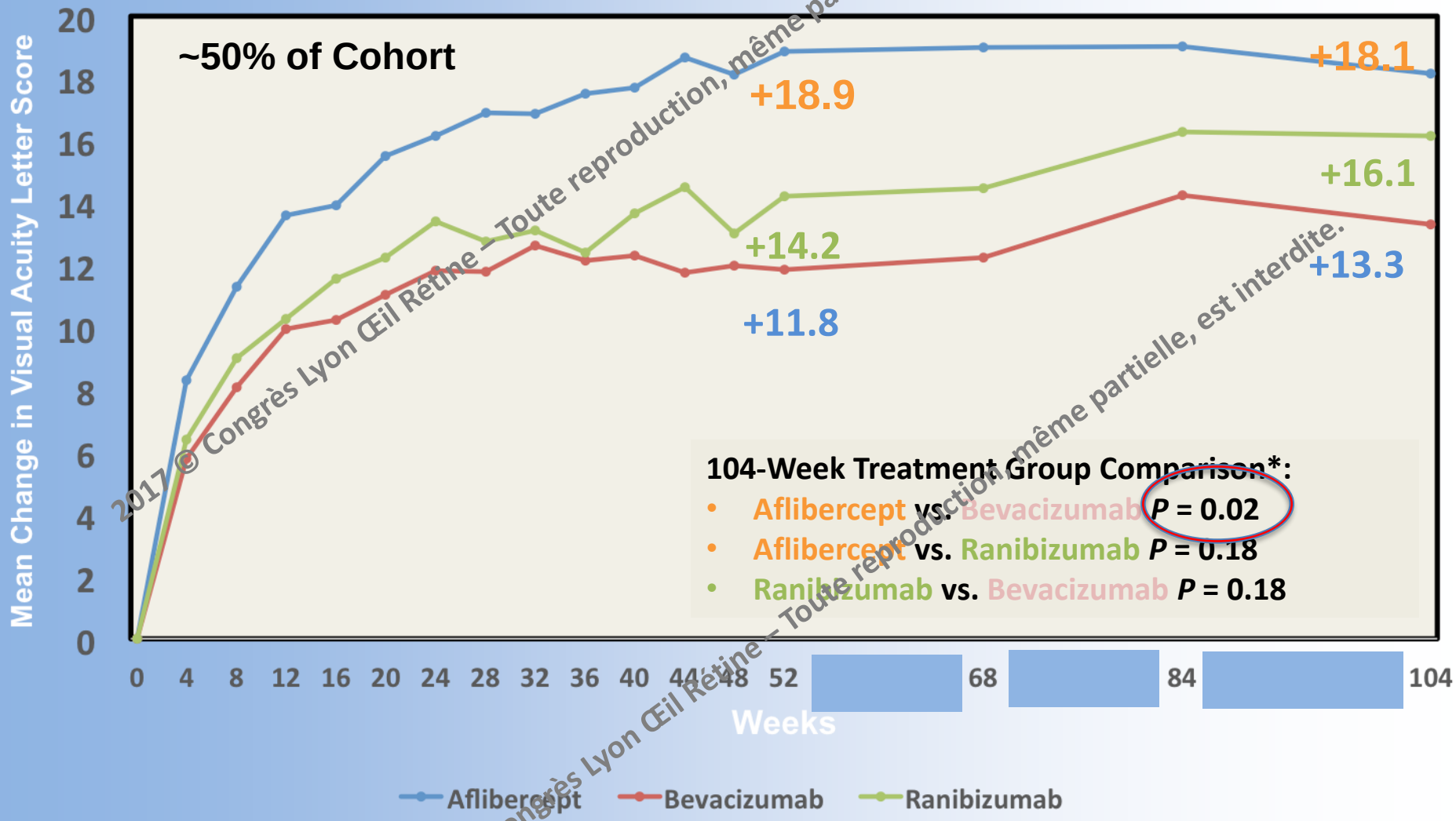
Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity ***20/50 or Worse***



[52-Week: A vs. B *P* < 0.001 / A vs. R *P* = 0.003 / R vs. B *P* = 0.24]

* *P*-values adjusted for baseline visual acuity and multiple comparisons

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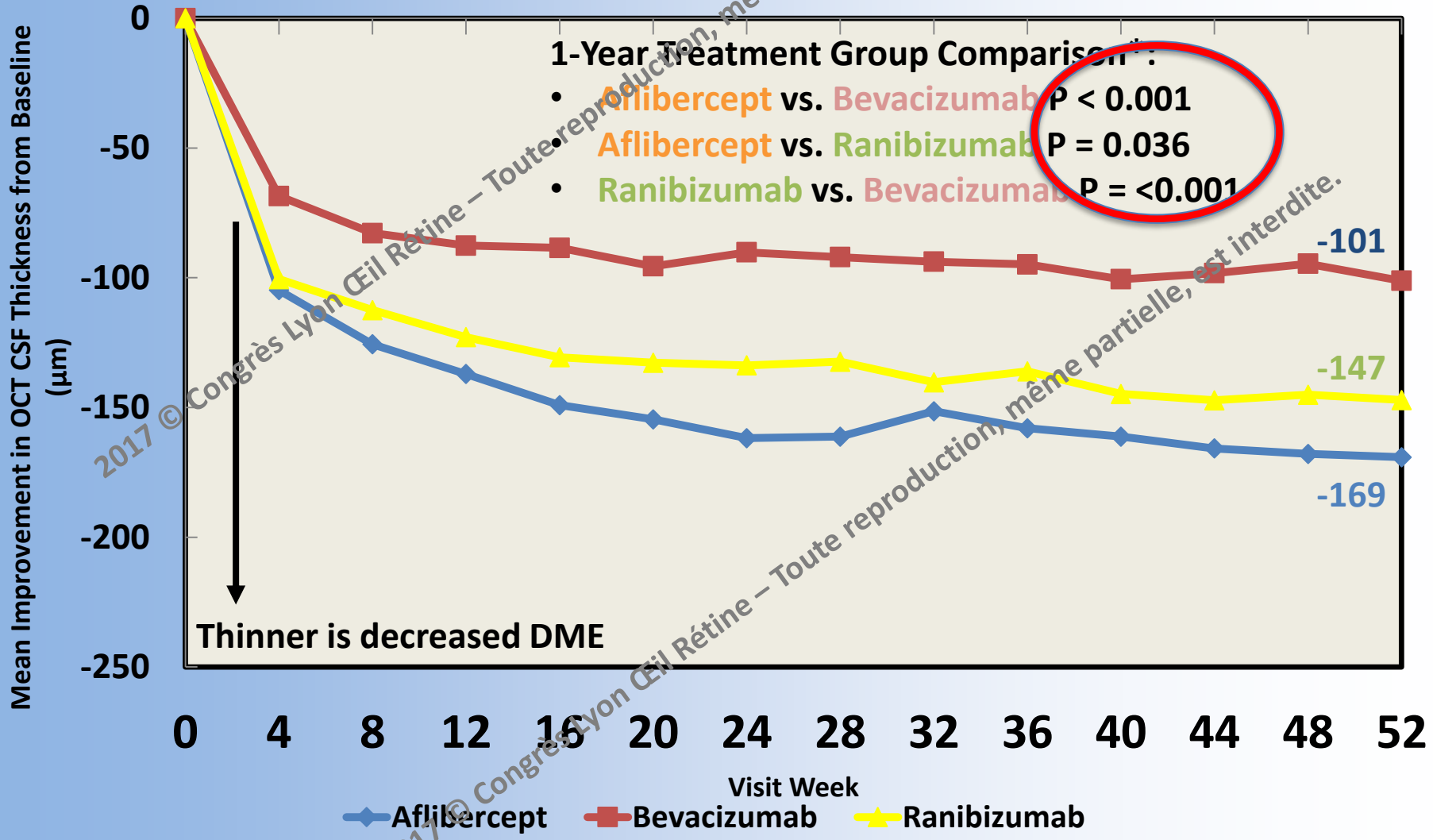
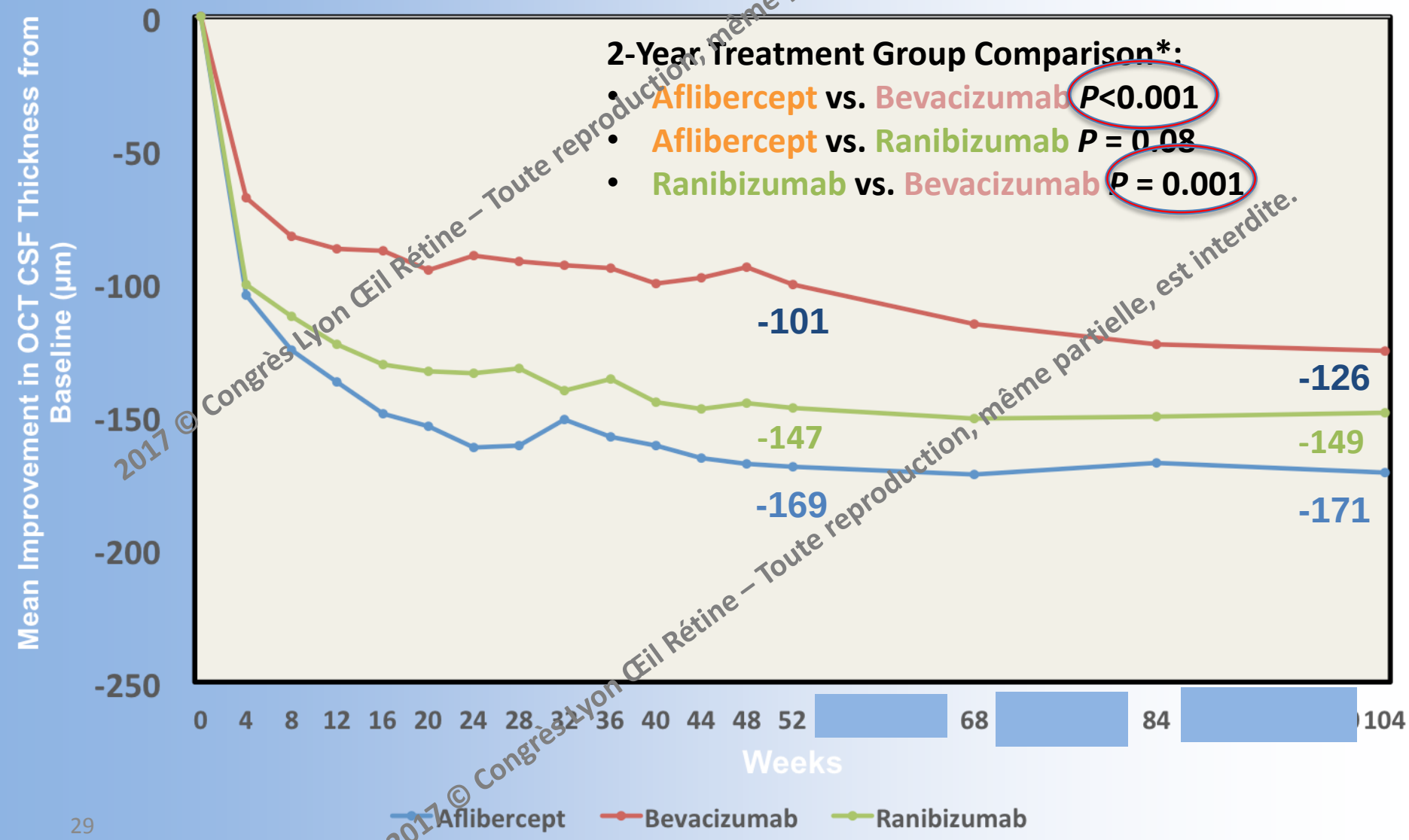
Overall Mean (µm) Change in OCT CST Over Time



* *P*-values adjusted for baseline visual acuity, OCT central subfield thickness, and multiple comparisons

Mean Change in OCT CST Over 2 Years

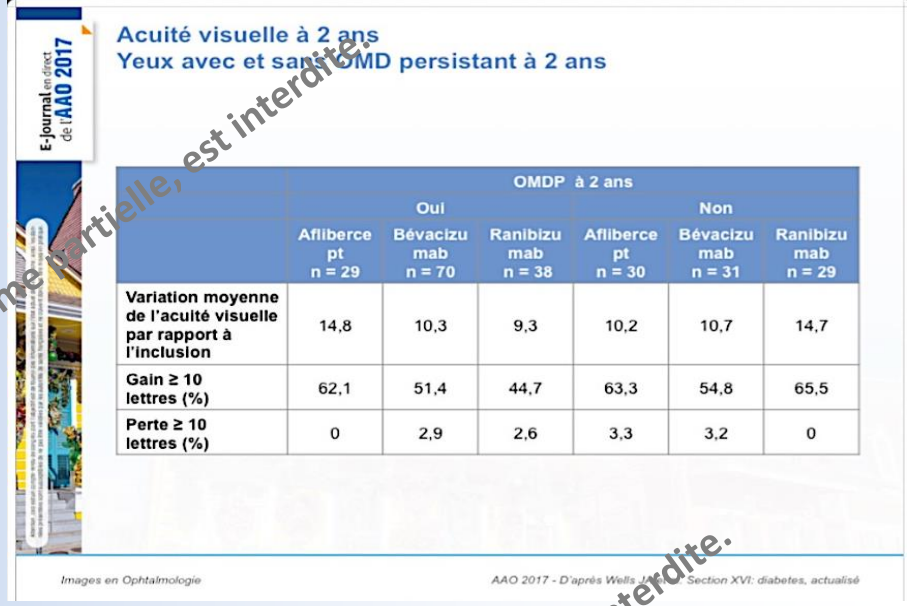
Full Cohort



* *P*-values adjusted for baseline visual acuity, OCT central subfield thickness, and multiple comparisons

OMD persistant

Wells JA et Al AAO 2017



	OMDP à 2 ans					
	Oui			Non		
	Aflibercept n = 29	Bévacizumab n = 70	Ranibizumab n = 38	Aflibercept n = 30	Bévacizumab n = 31	Ranibizumab n = 29
Variation moyenne de l'acuité visuelle par rapport à l'inclusion	14,8	10,3	9,3	10,2	10,7	14,7
Gain ≥ 10 lettres (%)	62,1	51,4	44,7	63,3	54,8	65,5
Perte ≥ 10 lettres (%)	0	2,9	2,6	3,3	3,2	0

- OMD persistant : présent inclusion présent à 6 mois malgré IVT anti-VEGF (546 patients)
  - Prévalence à 6 mois de traitement / molécule (Afli, Rani, Béva)
  - % patients avec OMD persistant à 2 ans « Chronicité) / molécule (Afli, Rani, Béva)
  - Gain de 10 lettres OMDP à 2 ans / molécule (Afli, Rani, Béva)

	Aflibercept	Ranibizumab	Bévacizumab
OMD Persistant à 24 se	32%	41%	66%
OMD Persistant à 2 ans	44%	54%	68%
Gain ≥ 10 letres à 2 ans OMDP	62%	51%	45%

Moindre passage à la chronicité à 2 ans sous Aflibercept

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Combinaisons ?

Protocole U

November 11, 2017

Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema

A DRCR Network Phase 2 Randomized Clinical Trial

Raj K. Maturi, MD[1]; Adam R. Glassman, MS[2]; Danni Liu, MSPH[2]; et al

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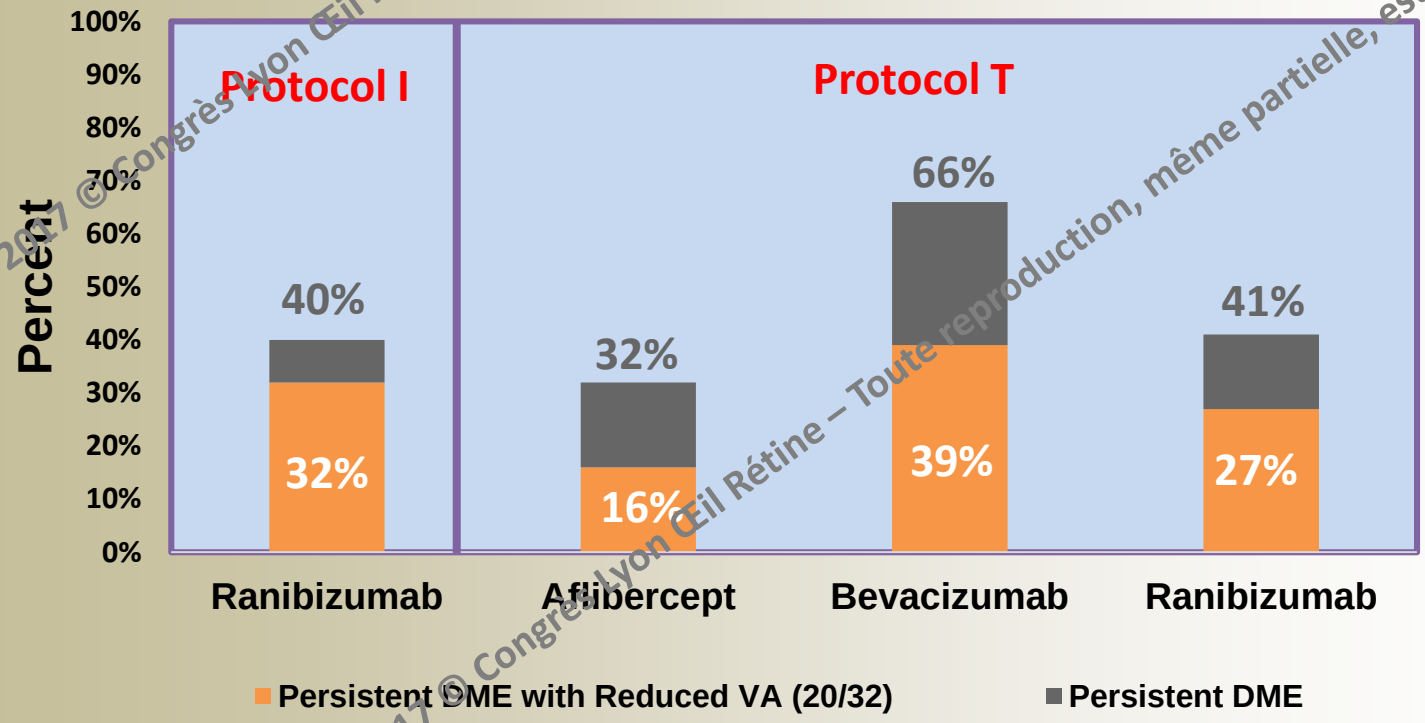
Objectif…

- Etude multicentrique , randomisée, N = 116 participants, N = 129 yeux
- Après au moins 6 IVT mensuelles d'anti-VEGF --> OMD persistant et AV réduite
- Critère de jugement principal: Variation moyenne d'AV à 24 S
- Critère de jugement secondaire: Variation moyenne CST (OCT) à 24 S



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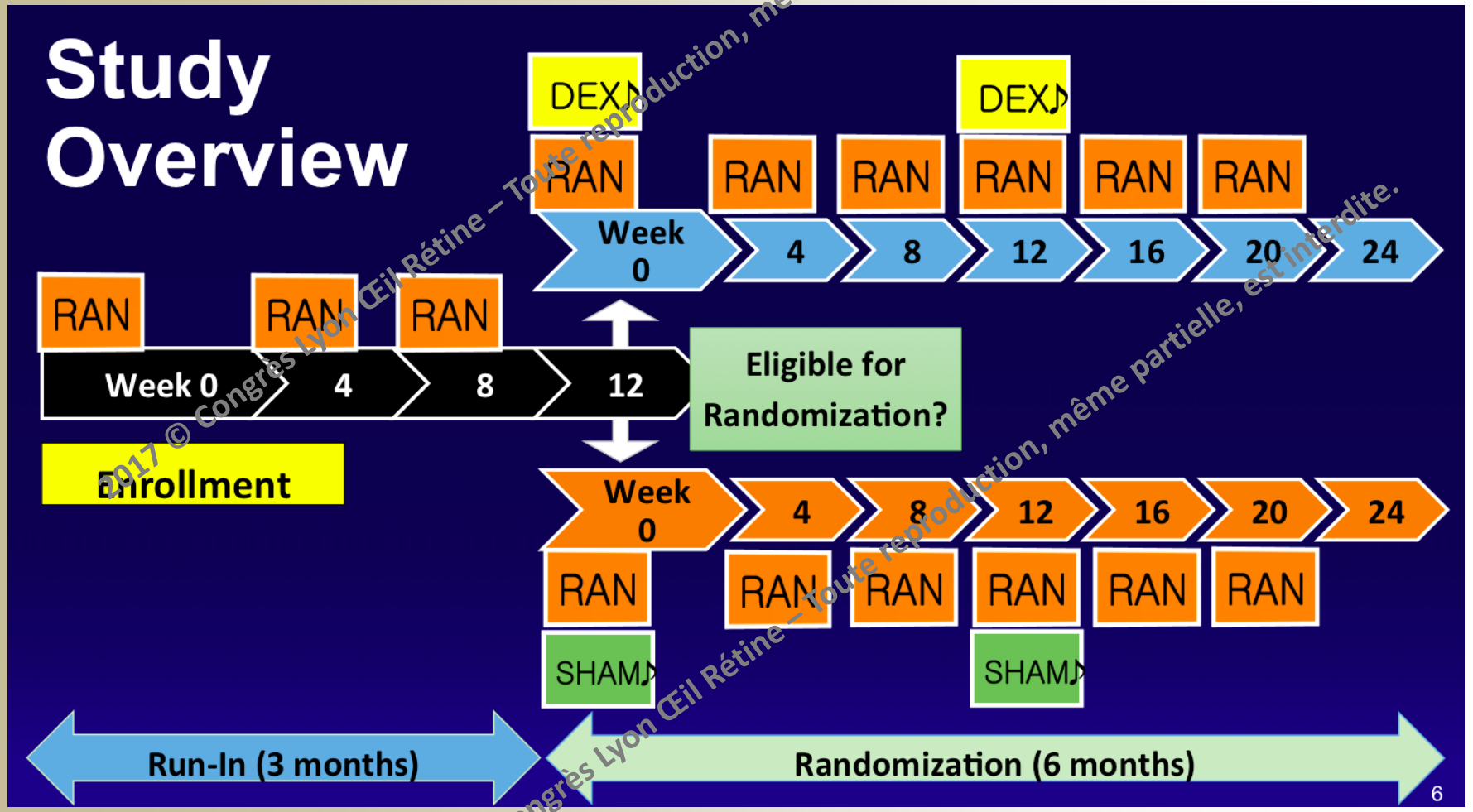
Study Overview



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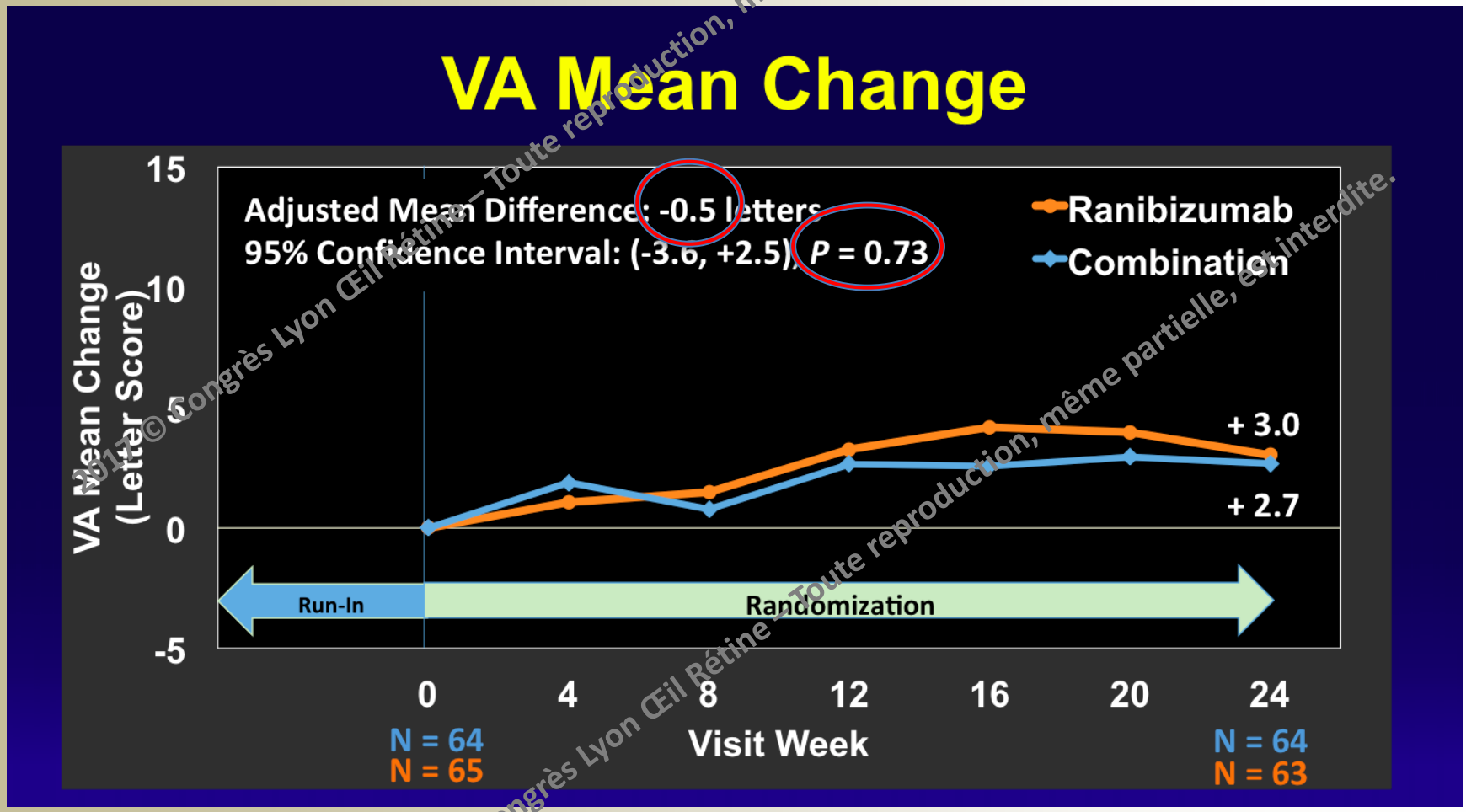
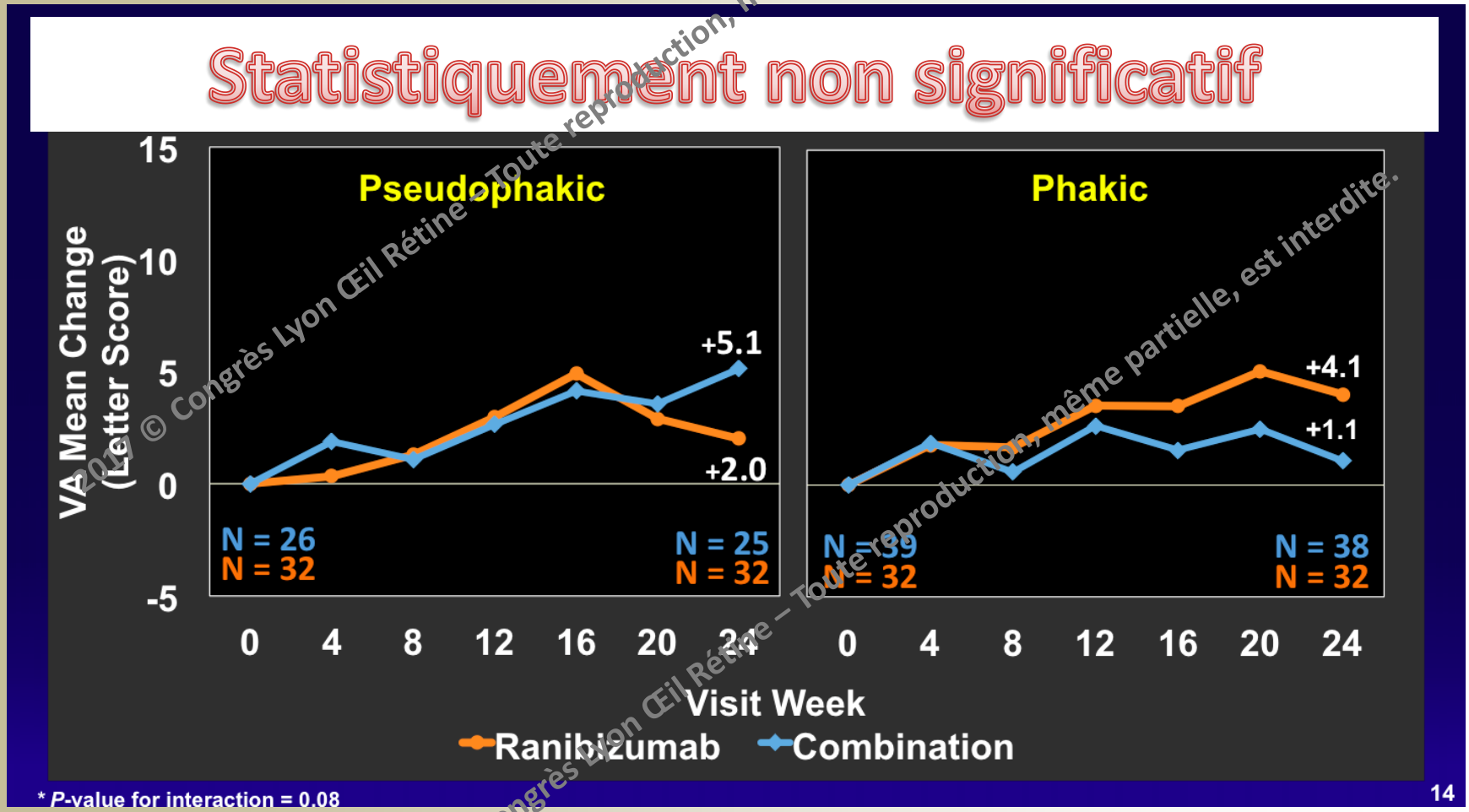
Gain moyen d'AV (1e critère principal)



Gain moyen d'AV Fct (statut cristallinien)



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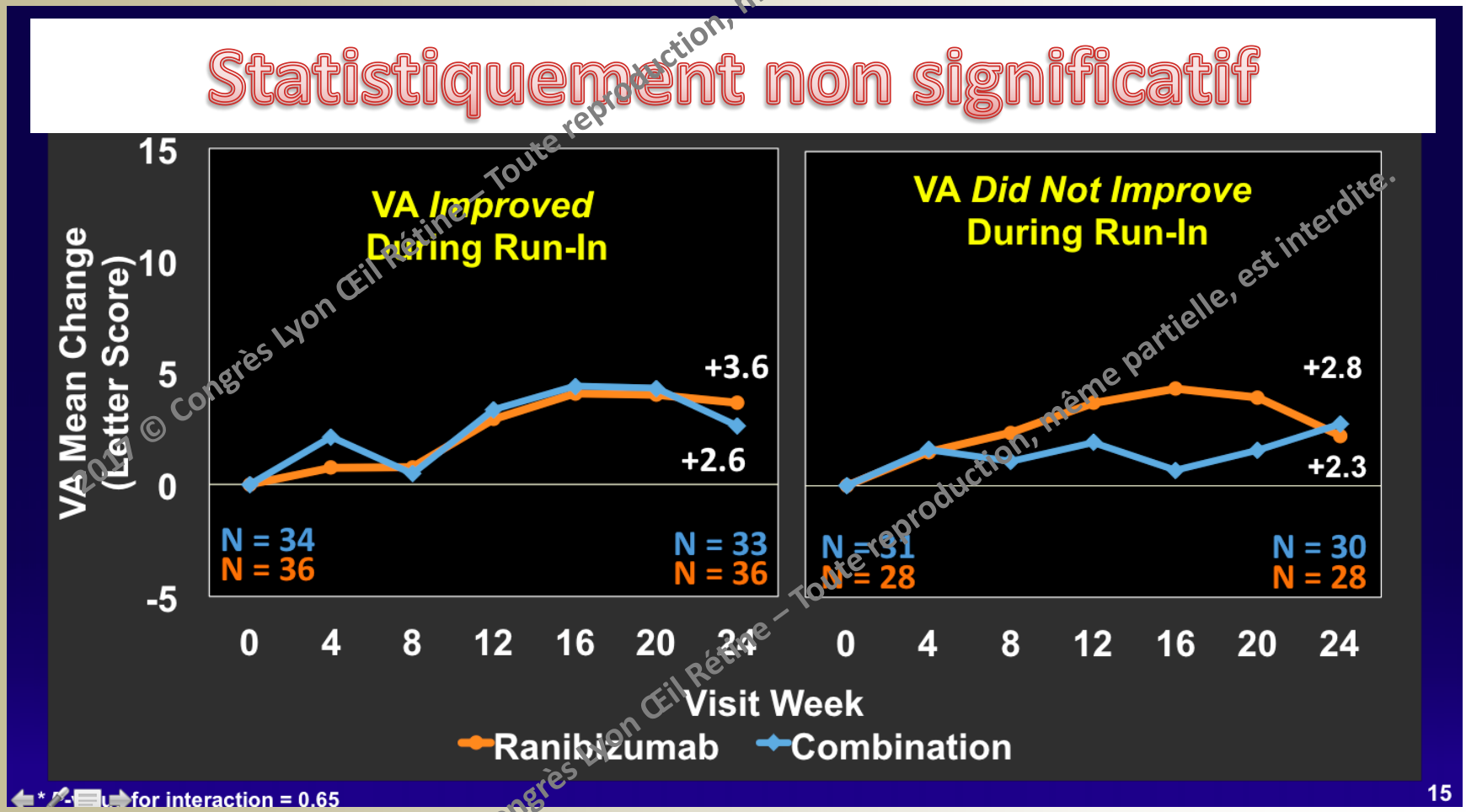
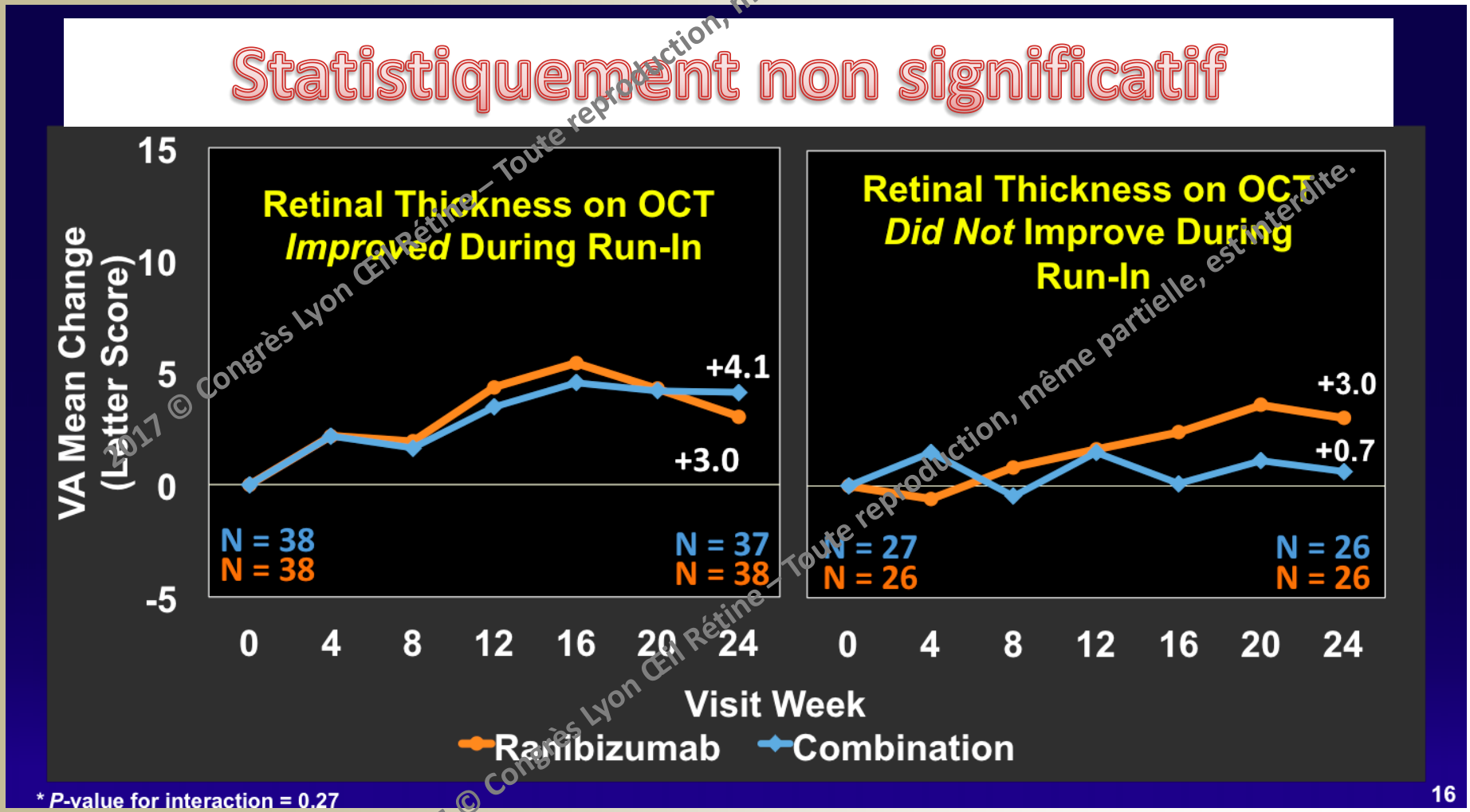
Gain moyen AV Fct (réponse Ranibizumab Run-in)

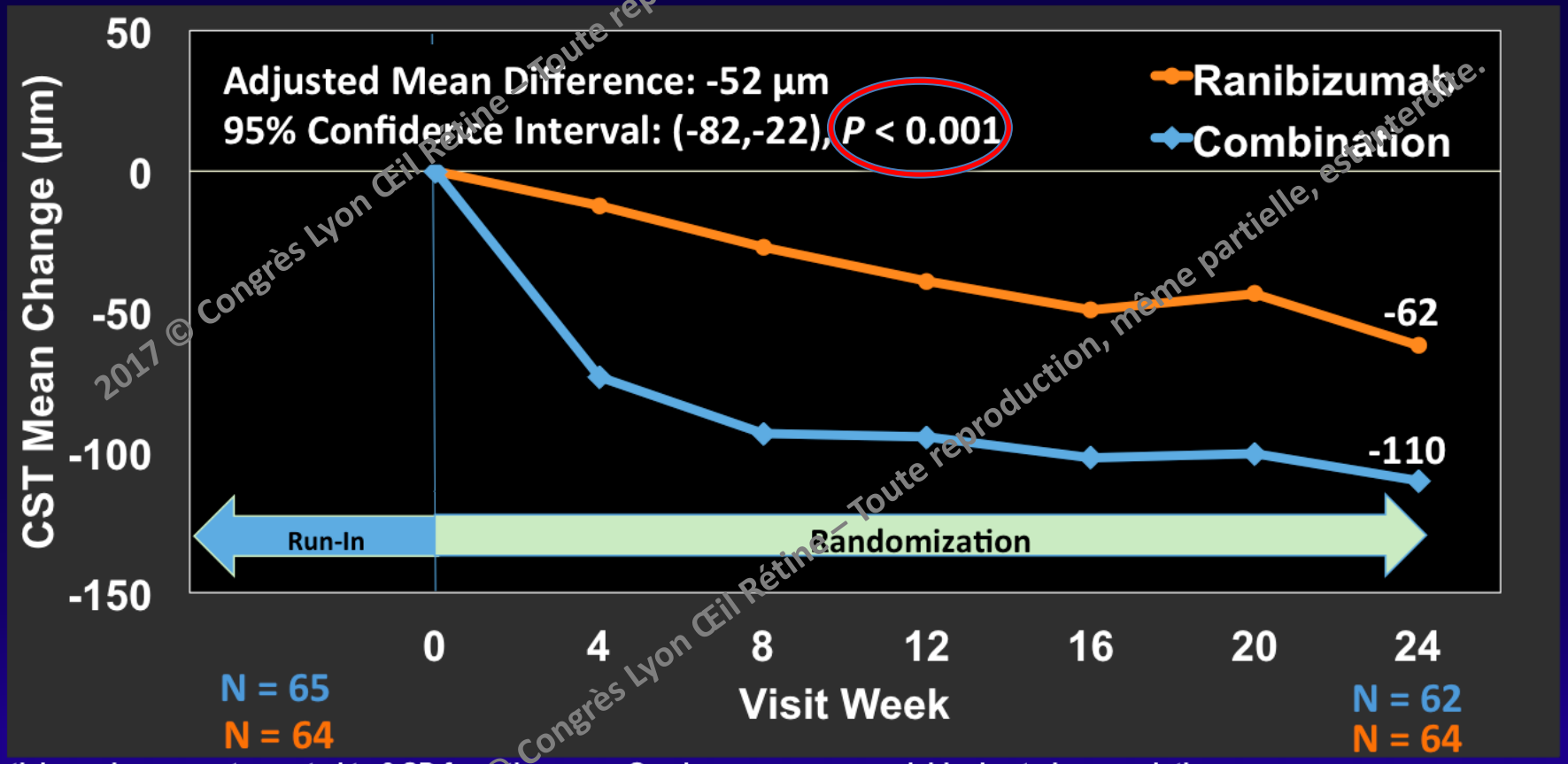


Gain moyen d'AV Fct (réponse OCT initiale)



* *P*-value for interaction = 0.27

Résultats anatomiques OCT (Crit secondaire)



*Outlying values were truncated to 3 SD from the mean. One image was nongradable due to low resolution.

Conclusion

- Le gain moyen d'AV: Pas de différence à 6 mois
- Réduction OMD:
  - Meilleure réponse groupe Rani+ Dexa > Rani+ Sham à 6 mois
- Résultat non extrapolables aux autres anti-VEGF !
- Courte durée de l'étude!

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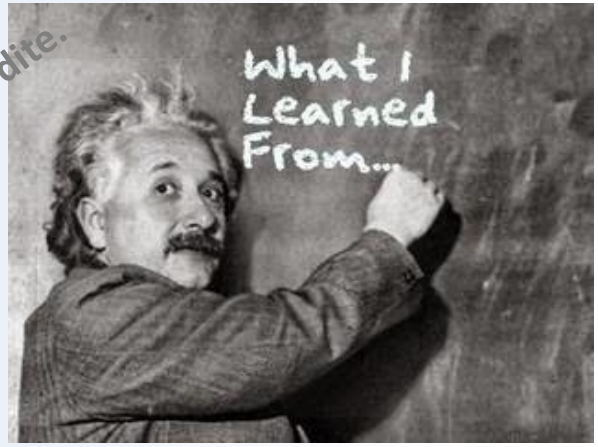
POUR OPTIMISER LE TRAITEMENT



1. Traiter **PRÉCOCEMENT (7/10, P3 ?)**
2. Traiter **INTENSIVEMENT** la première année
3. **PERSONNALISER** le suivi évite de sur-traiter: PRN / T&E
4. Traiter les **FACTEURS SYSTEMIQUES**
5. **LASER FOCAL ?** mais sans effet (nb d'injections / gain AV)
6. **LA PERIPHERIE (PPR++ / OU …)**
7. **RESPECTER L' AMM**
   - **Ranibizumab (Lucentis) :**
     - 3 IVT mensuelles -> IVT jusqu'à AV maximale et / ou assèchement sur OCT
     - A la discrétion du médecin : PRN basé sur AV ou OCT , Mensuel et T&E
   - **Aflibercept (Eylea):**
     - 5 IVT mensuelles puis q8 jusqu'à 52 se , Visites de contrôle pas obligatoires.
     - Espacement possible selon AV et OCT , PRN , Mensuel ..
   - **Bevacizumab (Avastin) : hors AMM.**

Merci pour votre écoute attentive…

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