L'ANTI-ANGIOPOÏETINE 2
Un traitement d'avenir pour la DMLA et l'OMD ?

2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

Laurent KODJIKIAN

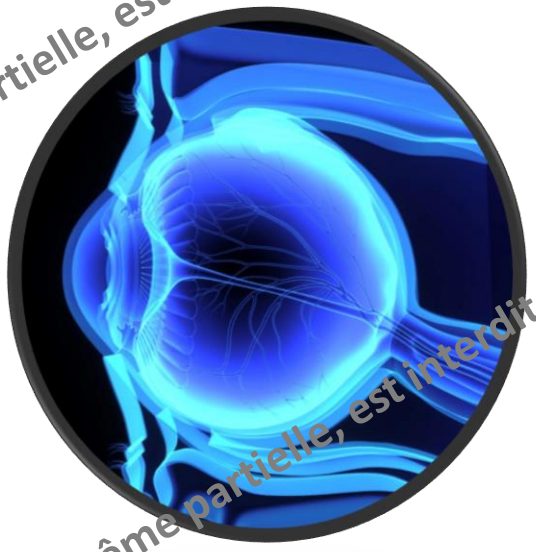
CHU de la CROIX-ROUSSE
UMR-CNRS 5510 Matéis
Lyon, France

Lyon 1

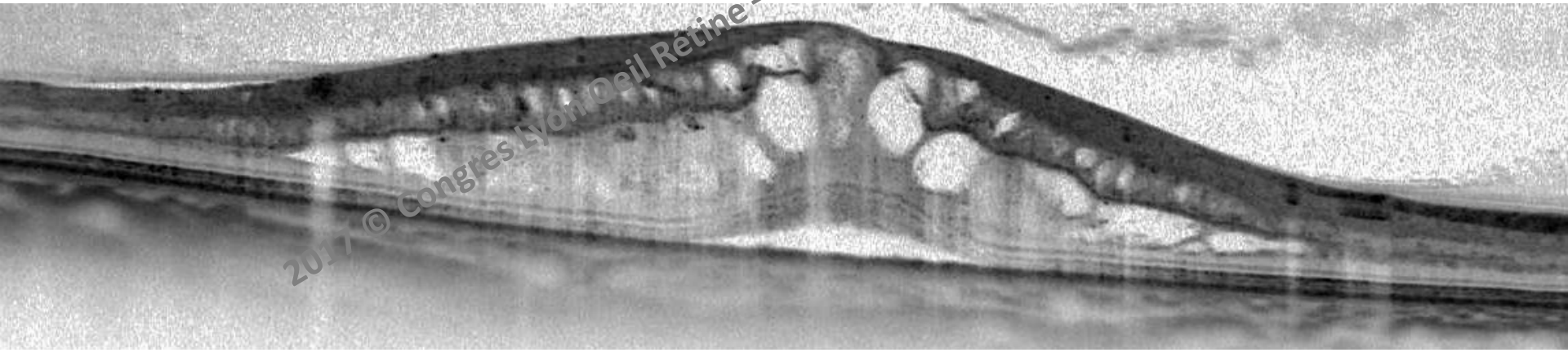
Hôpitaux de Lyon

Déclaration d'intérêts

- AbbVie
- Alcon
- Allergan
- Bayer
- Horus
- Krys
- Roche
- Novartis
- Théa

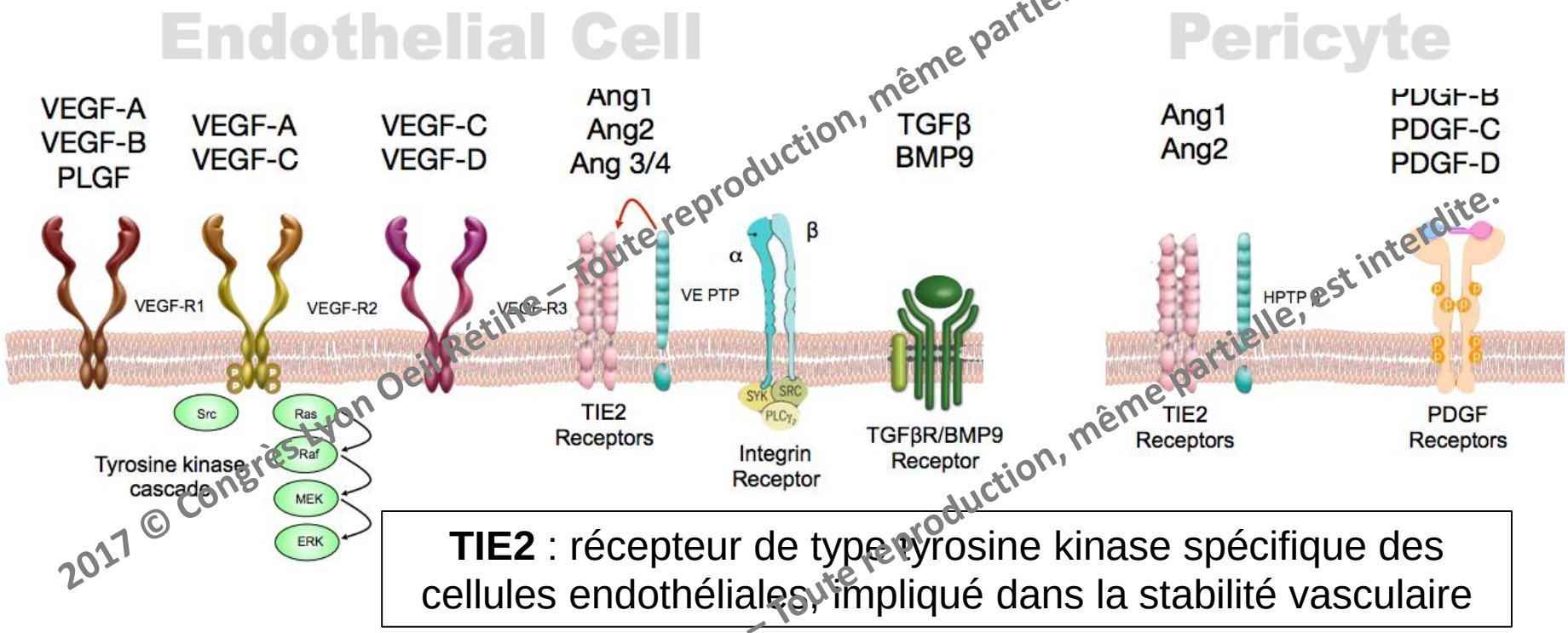


2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.



2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

Les voies de développement clinique en DMLA

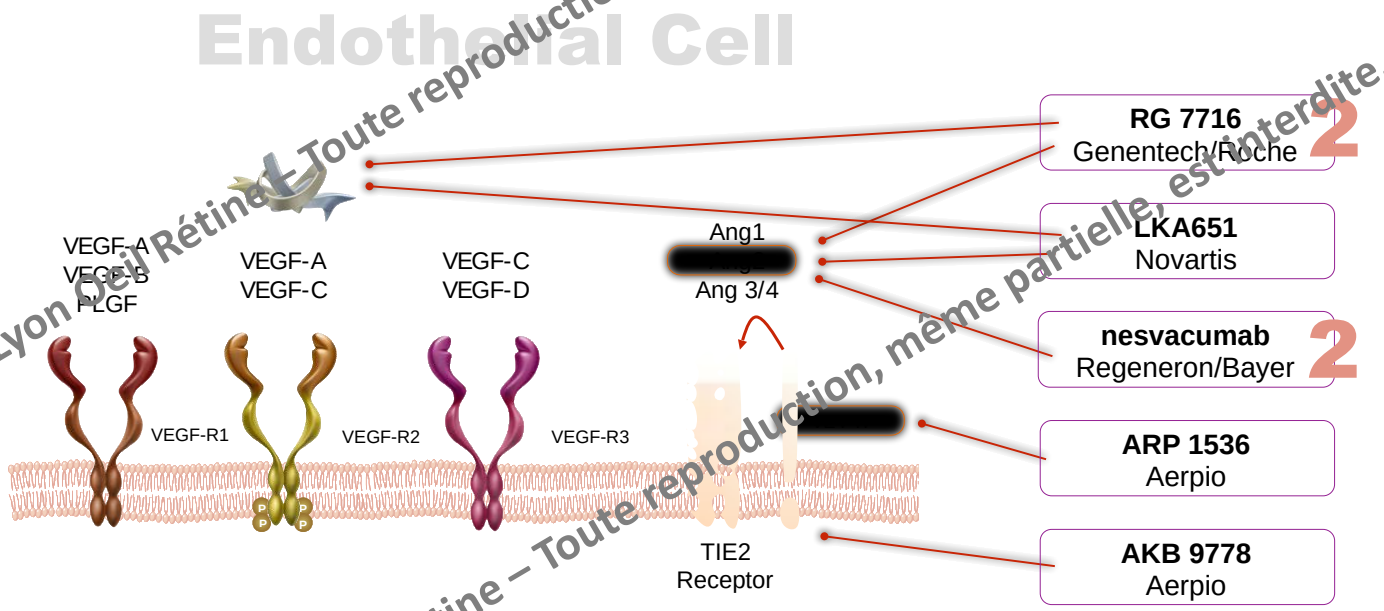


TIE2 : récepteur de type tyrosine kinase spécifique des cellules endothéliales, impliqué dans la stabilité vasculaire

- Ang1: active récepteur Tie2 ➔ maintient homéostasie et jonctions serrées
- Ang2 est sécrété en conditions pathologiques par les cellules endothéliales & phosphoryle le récepteur Tie2 ➔ empêche Ang1 d'avoir son action bénéfique ➔ <u>↑ angiogenèse et perméabilité vasculaire</u>
- Ac Anti-Ang2: vient en compétition avec Ang2 et maintient action positive de Ang1

La voie des Angiopoïétines

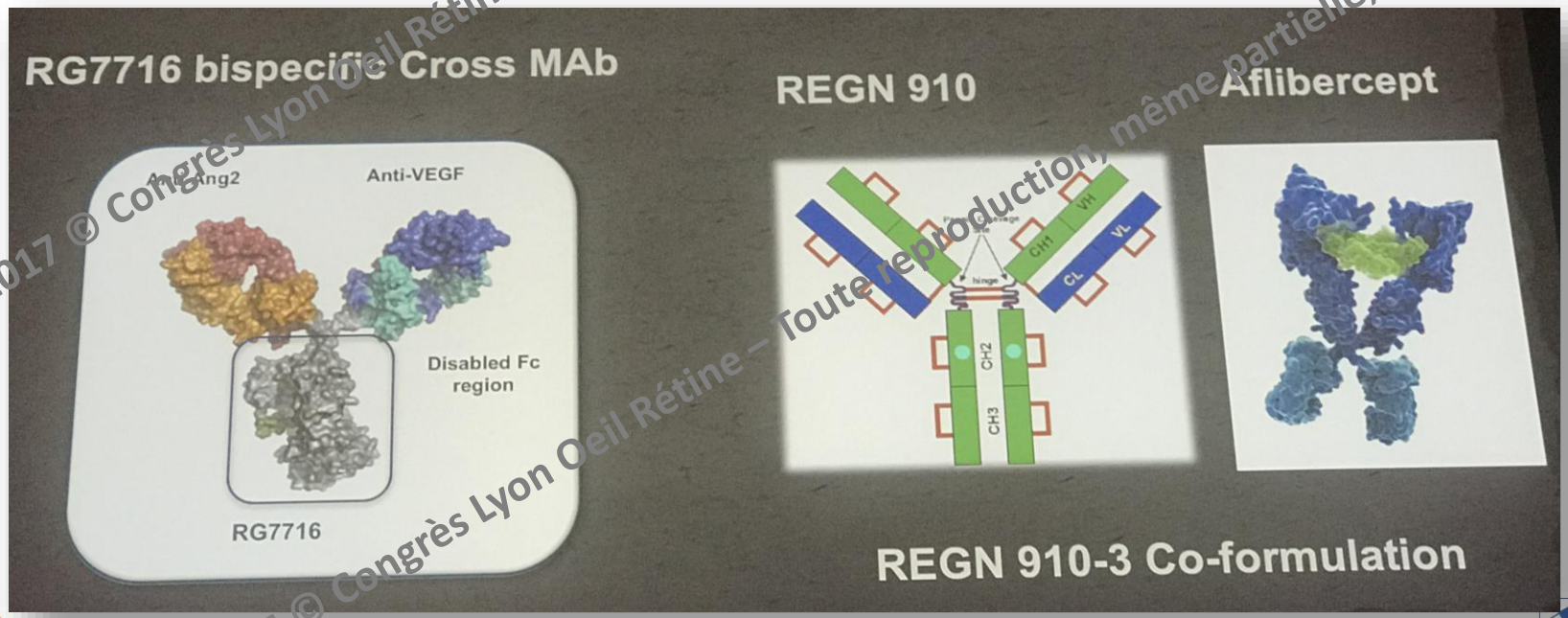
Angiopoieten Pathways



2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.
2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

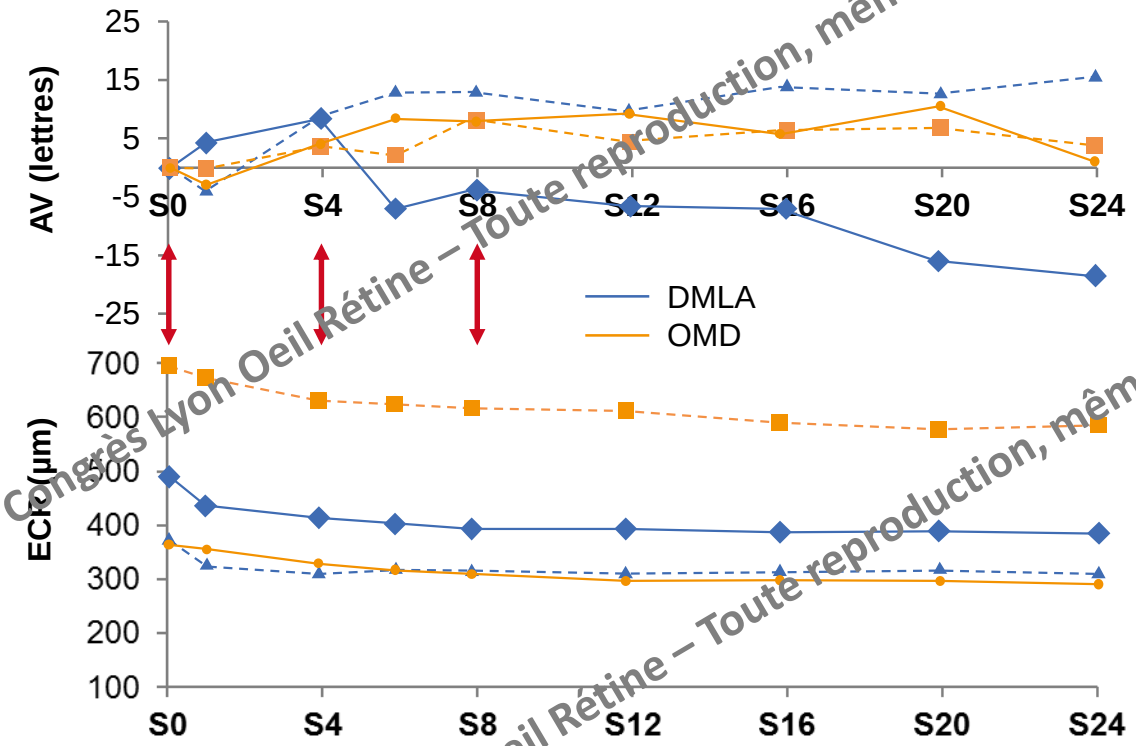
2 molécules en voie de développement

- **Nesvacumab** des laboratoires Regeneron/Bayer
  - ➢ *qlq mois d'avance dans son développement clinique*
- **RG 7716** des laboratoires Genentech/Roche



Etude de phase I associant un anti-VEGF à un inhibiteur d'Ang2: nesvacumab+aflibercept

Évolution de l'AV et de l'ECR dans la cohorte nesvacumab 3 mg + aflibercept 2 mg



	S12	S24	
■	+4	+2	
●	+9	-1	
▲	+10	+15	*
◆	-8	-22	*

Pas de retraitement

	S12	S24	
■	-97	-130	
●	-71	-71	
▲	-66	-59	*
◆	-113	-118	*

** Naïf de traitement.*

- Absence de toxicité de dose du nesvacumab ou d'effet indésirable oculaire rapportés

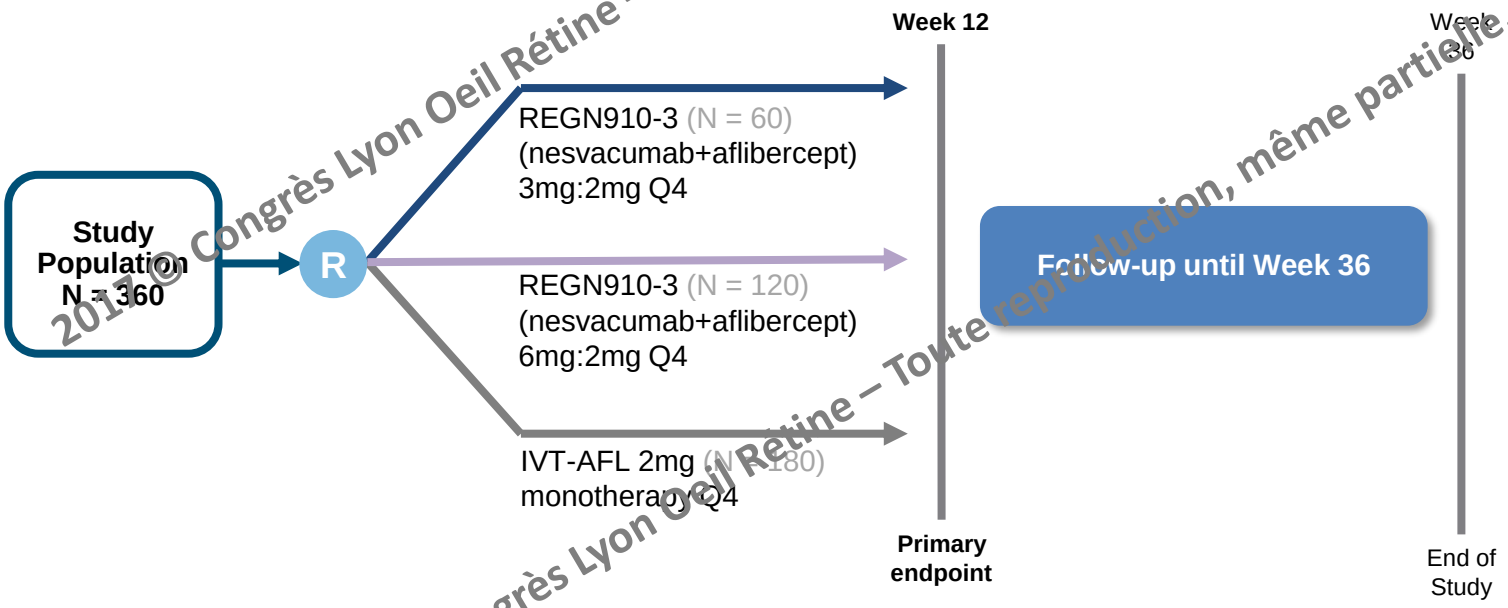
AAO 2016 - D'après Csaky KG – Section X : First-time results of clinical trials, actualisée

2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.
2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

Etude de phase II nesvacumab+aflibercept
ONYX - DMLA

Study title: A Randomized, Double-Masked, Active-Controlled, Phase 2 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal REGN910-3 in Patients With Neovascular Age-Related Macular Degeneration

Objective: To compare the efficacy of intravitreal (IVT)-administered REGN910-3 compared to intravitreal aflibercept in improving BCVA in patients with AMD



Study design:
Randomized, multicenter, double-masked, active controlled, parallel-group study

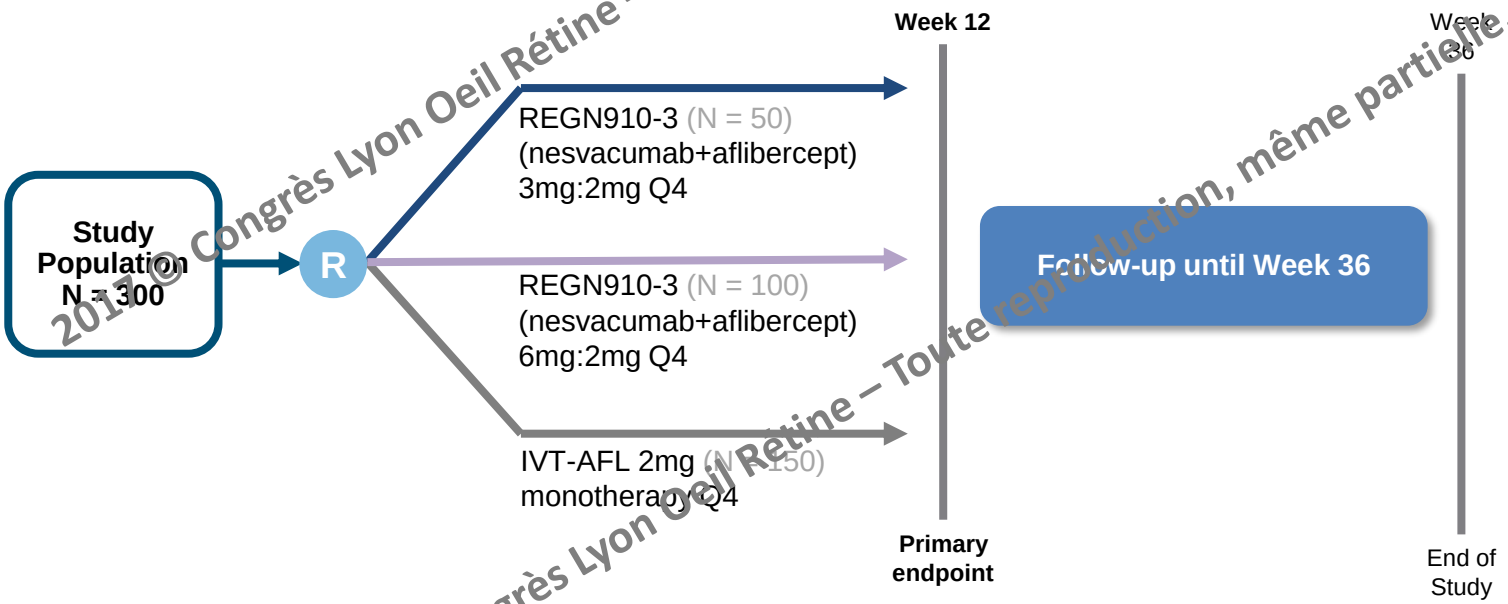
Primary endpoint:
Change from baseline BCVA (ETDRS) letter score at week 12

https://clinicaltrials.gov/ct2/show/NCT02713204?term=regn910-3&rank=2
https://clinicaltrials.gov/ct2/show/NCT02712008?term=regn910-3&rank=3

Etude de phase II nesvacumab+aflibercept
RUBY- OMD

Study title: A Randomized, Double-Masked, Active-Controlled, Phase 2 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal REGN910-3 in Patients With Diabetic Macular Edema

Objective: To compare the efficacy of intravitreal (IVT)-administered REGN910-3 compared to intravitreal aflibercept in improving BCVA in patients with diabetic macular edema (DME).



Study design:
Randomized, multicenter, double-masked, active controlled, parallel-group study

Primary endpoint:
Change from baseline BCVA (ETDRS) letter score at week 12

https://clinicaltrials.gov/ct2/show/NCT02713204?term=regn910-3&rank=2
https://clinicaltrials.gov/ct2/show/NCT02712008?term=regn910-3&rank=3

Dernières nouvelles …

REGENERON

November 27, 2017

Regeneron Provides Update on EYLEA® (aflibercept) Injection and Nesvacumab (Ang2 Antibody) Combination Program

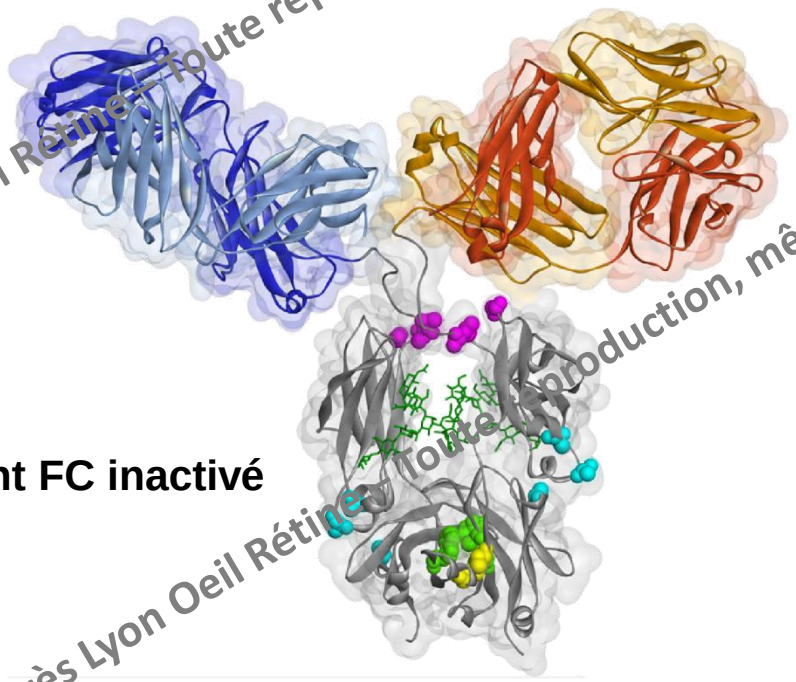
TARRYTOWN, N.Y., Nov. 27, 2017 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that results from two Phase 2 studies that added the angiopoietin2 (Ang2) antibody nesvacumab to EYLEA® (aflibercept) Injection did not provide sufficient differentiation to warrant Phase 3 development. The RUBY study evaluated patients with diabetic macular edema (DME) and the ONYX study evaluated patients with wet age-related macular degeneration (wet AMD). EYLEA results were consistent with findings in previous clinical studies. There were no new safety signals in these studies.

Lyon 1

Hôpitaux de Lyon

Une molécule originale

- **Le RG7716 est un anticorps monoclonal bispécifique comprenant un fragment Fab anti-VEGF, un fragment Fab anti-Ang2 et un fragment Fc désactivé**

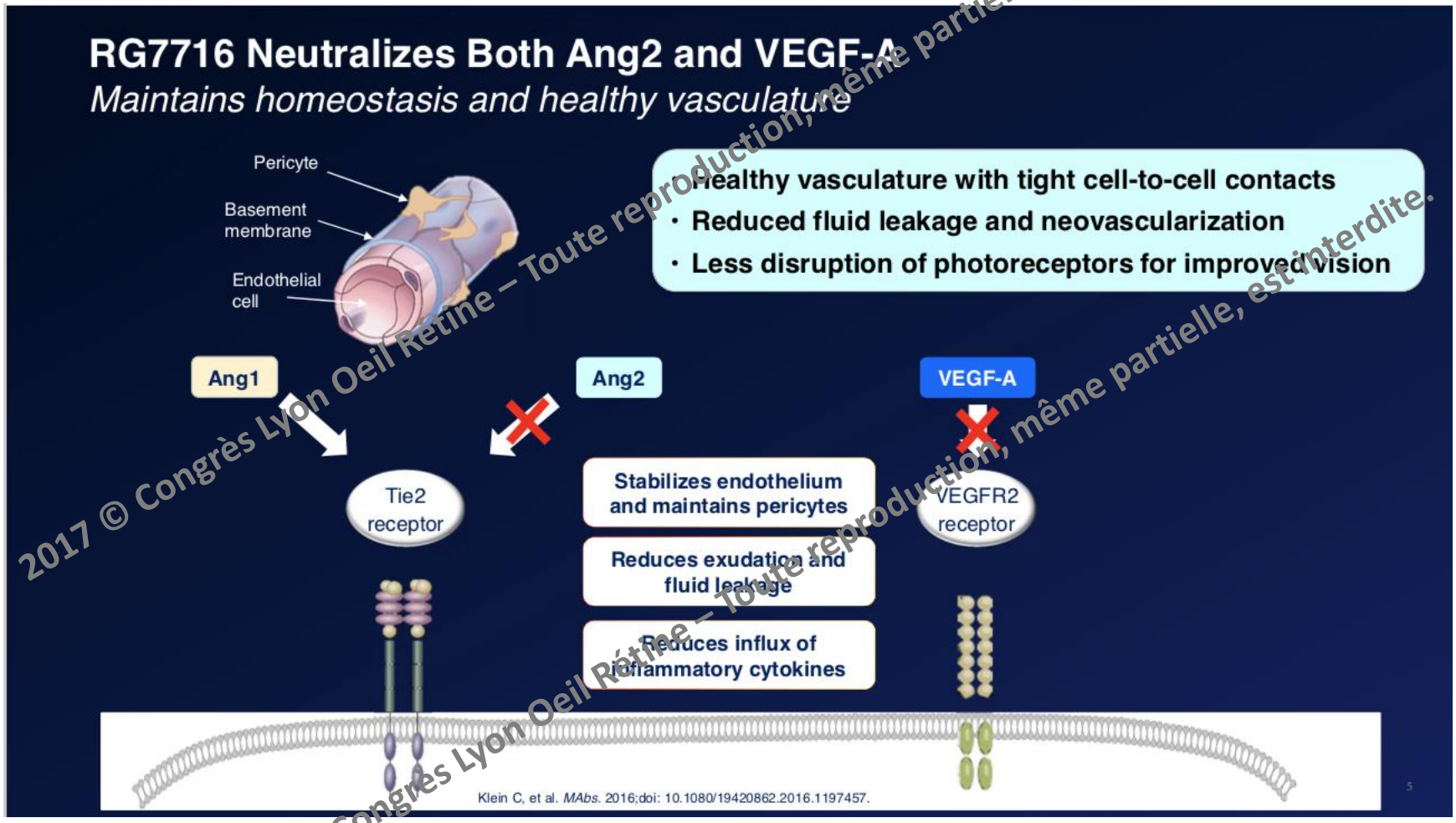


AAO 2017 - D'après Heier JS et al. Section XI: neovascular AMD, actualisé

Lyon 1

Hôpitaux de Lyon

Mécanismes d'action du RG 7716



Lyon 1

Hôpitaux de Lyon

Phase I

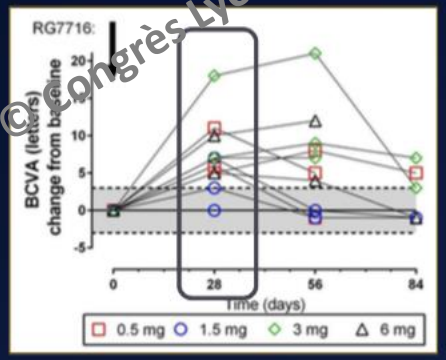
RG7716 Ph1 Safety / Tolerability and Efficacy Summary

Treatment refractory patients with average disease duration of 2.9 years

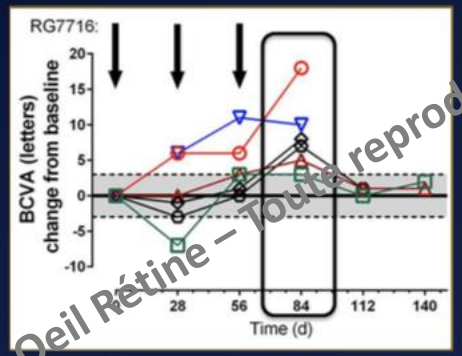
Safety

- Single and multiple dose injections were safe and well tolerated up to the highest dose tested
  - No dose limiting event was observed
  - No unexpected AEs related to the procedure of IVT injection or progression of the disease

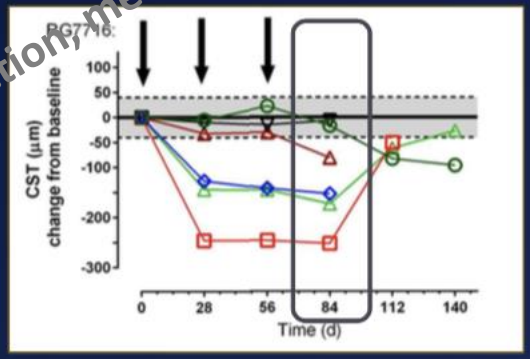
Efficacy: 28 Days after last dose



Single Dose
Median change of **+7 letters**



Multiple Dose (6mg)
Median change of **+7.5 letters**



Multiple Dose (6mg)
Median CST Decrease **-117 µm**

11

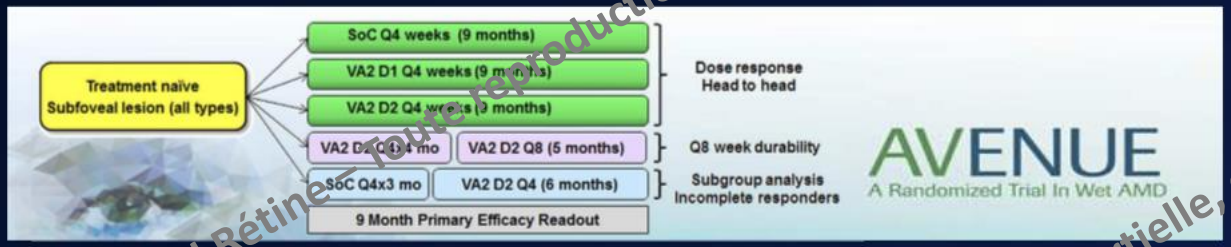
Lyon 1

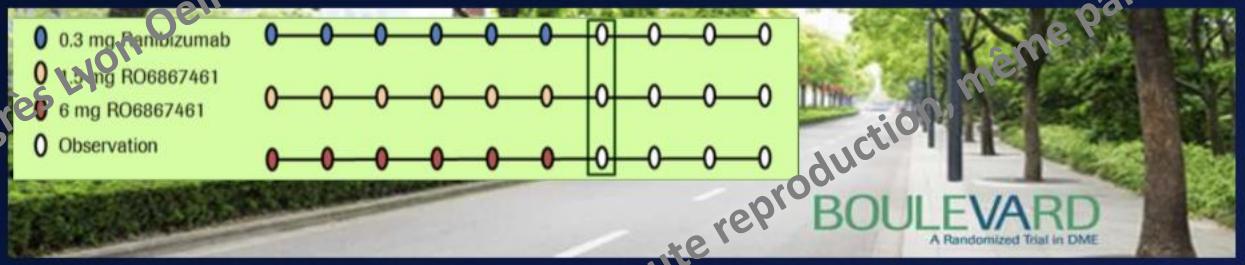
Hôpitaux de Lyon

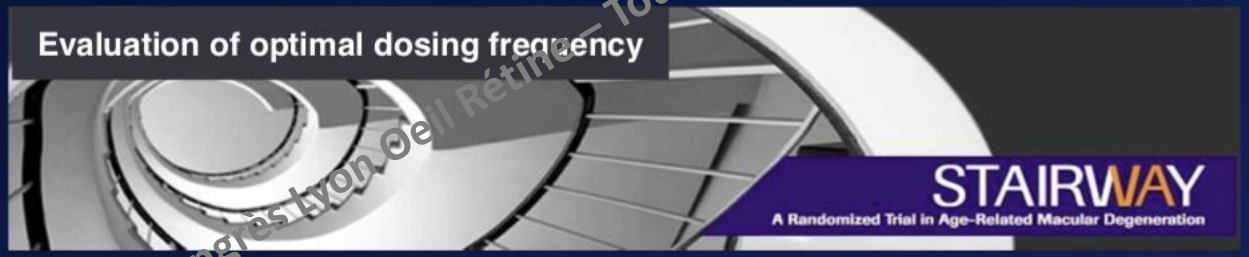
Phase II

Three Phase 2 Studies

Avenue (nvAMD), Boulevard (DME), Stairway (nvAMD Durability)







2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

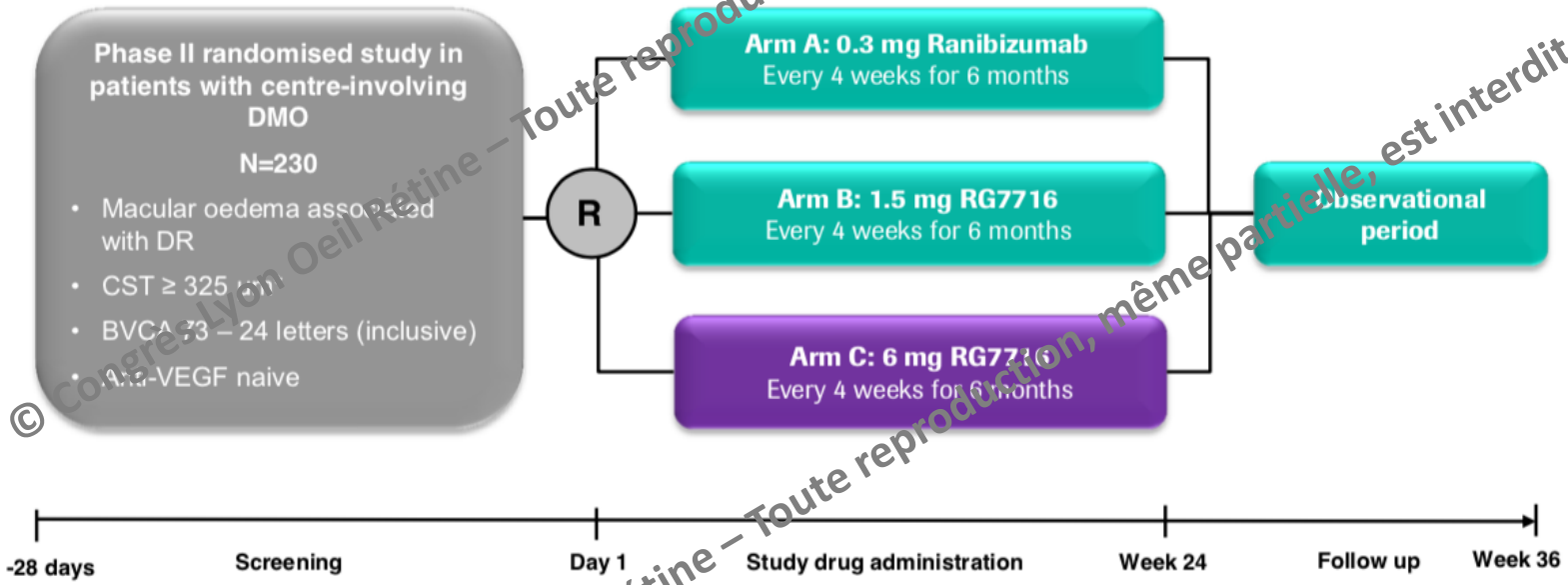
Lyon 1

Hôpitaux de Lyon

Phase II dans l'OMD

RG7716: Phase II BOULEVARD trial

Study design



Primary endpoints

- Mean change from baseline in BCVA at Week 24 using ETDRS-modified charts (results anticipated Q1 2018)

Study status and data communication

- Study fully enrolled and ongoing
- Data communication expected at congresses in 2018

Additional endpoints

- Percentage of participants gaining ≥ 15 letters from baseline in BCVA letter score
- Percentage of participants with BCVA letter score 20/40 or better and 20/20 or better
- Safety
- Pharmacokinetics

BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, early treatment diabetic retinopathy study;

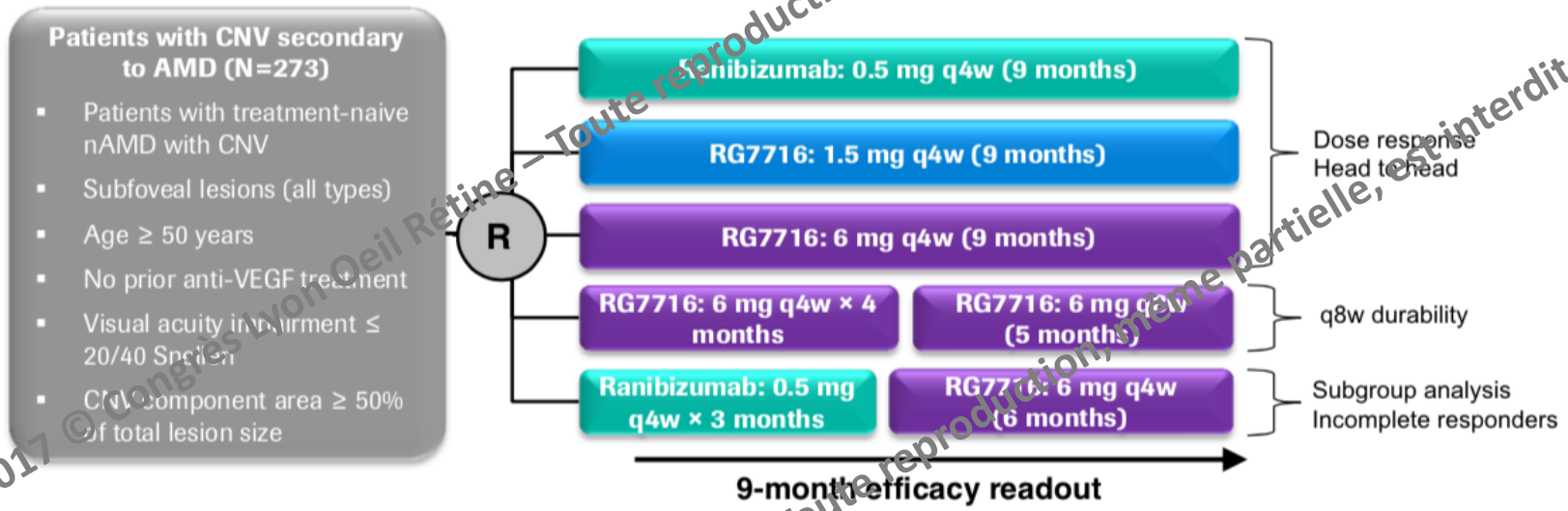
ClinicalTrials.gov (Date accessed: December2017 using "NCT02699450")

2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

Phase II dans la DMLA

RG7716: Phase II AVENUE trial

Study design



Primary endpoints

- Change from baseline in BCVA letter score (≤≈36 weeks)

Study status and data communication

- Study fully enrolled and ongoing
- Data communication expected at congresses in 2018

Additional endpoints

- Percentage of participants gaining ≥15 letters from baseline in BCVA letter score
- Percentage of participants with BCVA letter score 20/40 or better and 20/200 or worse
- Change from baseline in CFT and CST
- Safety (≤ ≈ 40 weeks)
- Pharmacokinetics

CFT, central foveal thickness; CST, central subfield thickness

ClinicalTrials.gov (Date accessed: December2017 using "NCT02484690")

2017 © Congrès Lyon Oeil Rétine – Toute reproduction, même partielle, est interdite.

CONCLUSION

- On peut espérer encore que les anti-ANG2 augmenteront l'efficacité mais surtout la durée d'action des anti-VEGF
- Dans l'attente des résultats de phase II de Roche …
- Lancement très probable d'études de phase III par Bayer