

NON RESPONDER TO ANTI-VEGF IN CNV

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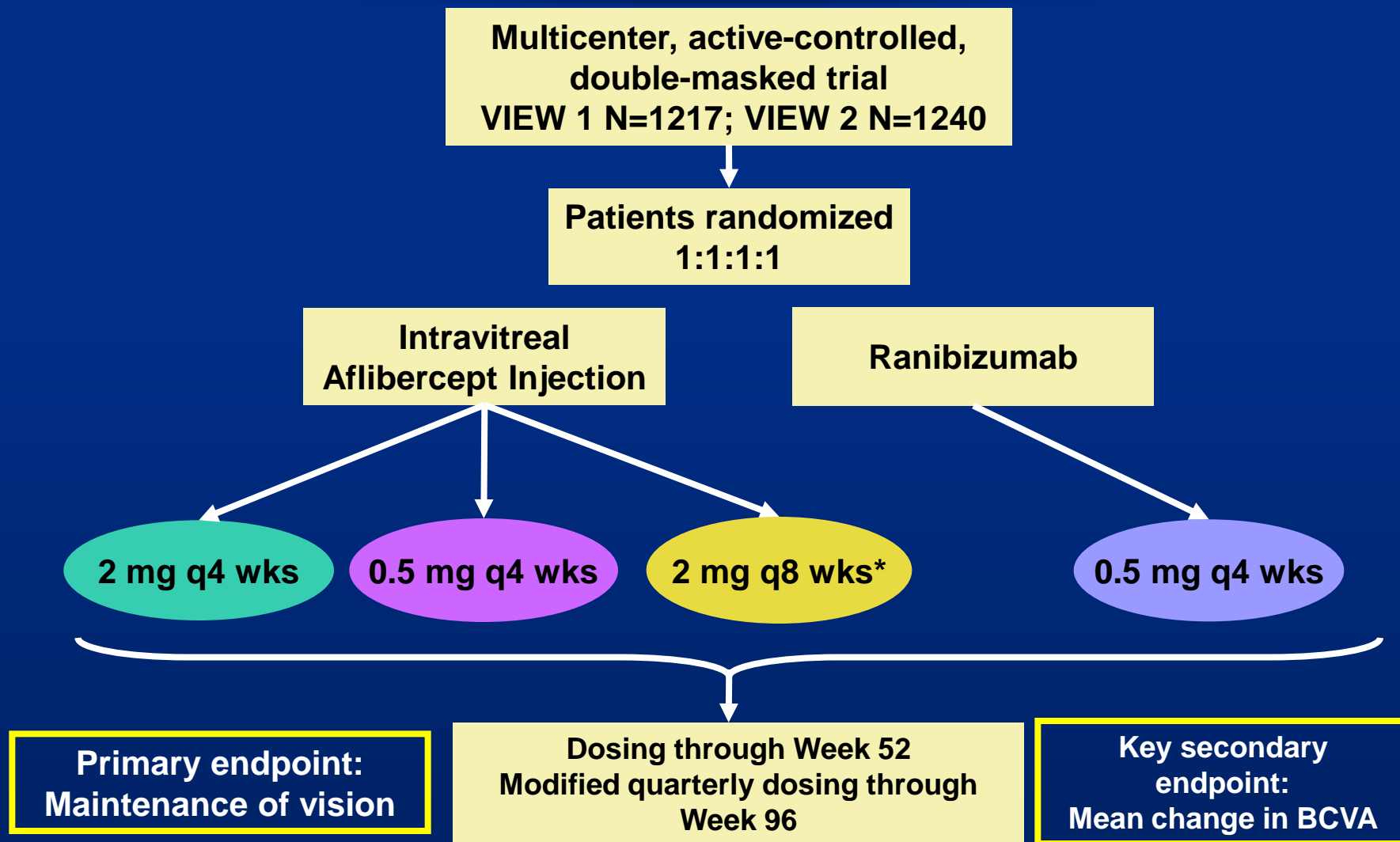
FINANCIAL DISCLOSURE

<u>SPONSOR</u>	
IMI	2003-2010
BAYER	2009-2013 (ongoing)
PFIZER	2010 (ongoing)
NOVARTIS	2011-2013 (ongoing)
CARL ZEISS	2011
PHARMAKOLOGIE BREMEN	2012 (ongoing)
PIXIUM	2013

Introduction

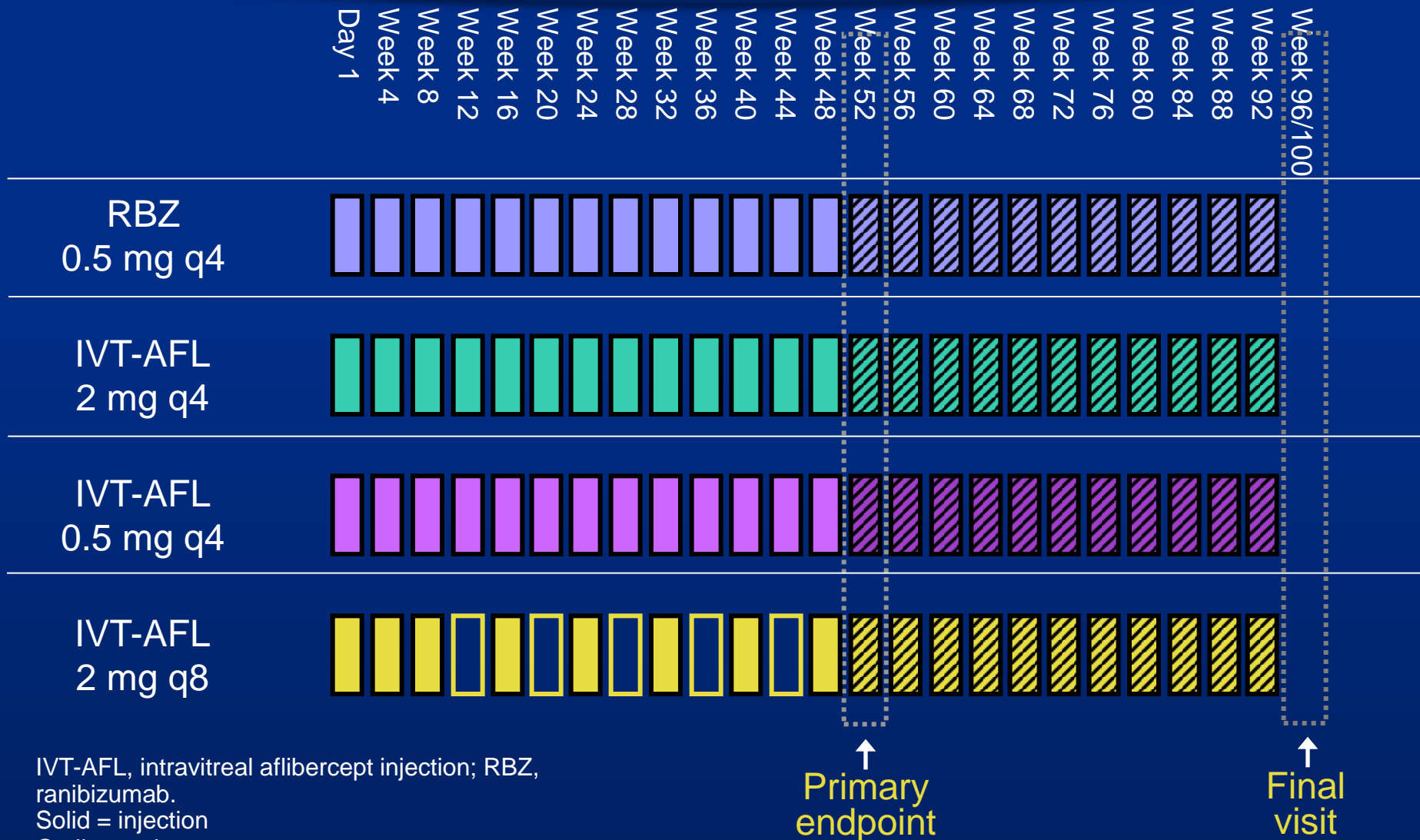
- Data indicate that subgroups of neovascular AMD have a poor prognosis
- The purpose of this presentation is to analyze the rational treatment of these patients

Study Design



*After 3 initial monthly doses. BCVA, best-corrected visual acuity.

Proactive Treatment Up To Week 52 – Thereafter Reactive Component



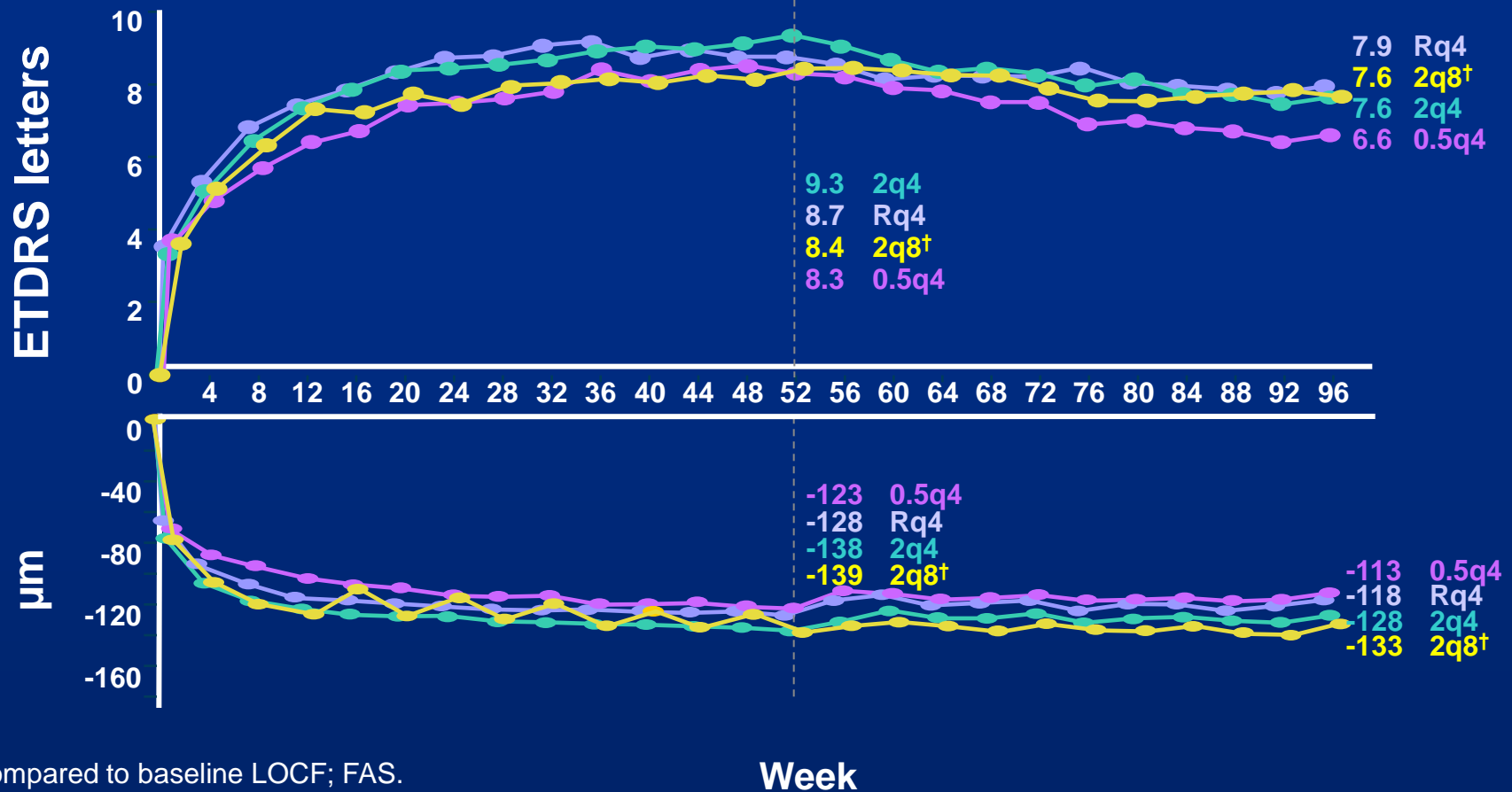
Retreatment Criteria for Year 2: Modified Quarterly Dosing

- Proactive or schedule-based treatment
 - 12 weeks since previous injection
- Reactive or symptom-based treatment
 - New or persistent fluid on optical coherence tomography (OCT)
 - Increase in central retinal thickness (CRT) of ≥ 100 μm compared to the lowest previous value
 - Loss of ≥ 5 ETDRS letters from the best previous score in conjunction with recurrent fluid on OCT
 - New onset classic neovascularization
 - New or persistent leak on fluorescein angiography
 - New macular hemorrhage

Overall Results

Slight Trend of Mean Vision Loss Observed in Year 2 for All Groups

Mean Change in BCVA and CRT Over 96 Weeks *



*Compared to baseline LOCF; FAS.

†After 3 initial monthly doses.

Rq4 n=595; 2q4 n=613; 0.5q4 n=597; 2q8 n=607.

VIEW 1: OCTs mandatory at baseline, Weeks 4, 12, 24, 36, and all visits from Weeks 52–96;

VIEW 2: OCTs mandatory at all visits.

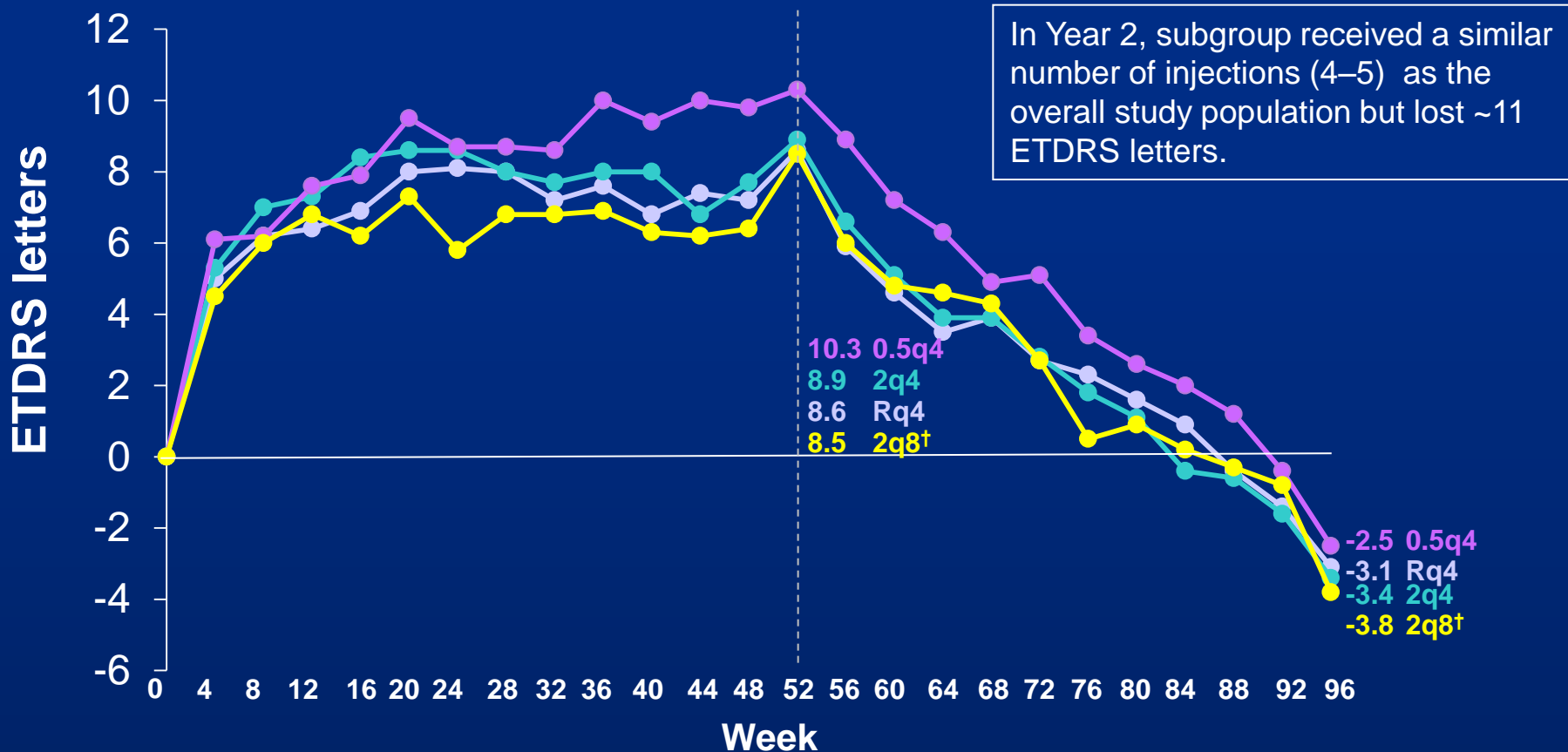
Exploratory Follow-up Phase (following Week 52)

What Drives the Slight Loss of Vision Under Reactive Treatment?

- **Hypothesis 1: There are some patients that lose significant visual acuity when switched from proactive to reactive dosing**
 - How many patients?
 - How many ETDRS letters are lost?
 - Is there any change in OCT preceding the drop in vision?
 - **Analysis strategy: Identify and analyze patients losing ≥ 5 letters between Week 52 and 96**
- **Hypothesis 2: Patients losing vision under a reactive scheme do not re-gain vision**
 - How many patients?
 - What were the visual outcomes for these patients during the proactive treatment phase up to week 52?
 - **Analysis strategy: Identify and analyze patients losing ≥ 5 letters between 2 consecutive visits between Week 52 and 64 with active treatment at the 2nd visit**

Hypothesis 1: ~20% of Patients Lost Vision From Year 1 to Year 2 With Reactive Dosing

Patients losing ≥ 5 letters between Week 52 and 96*



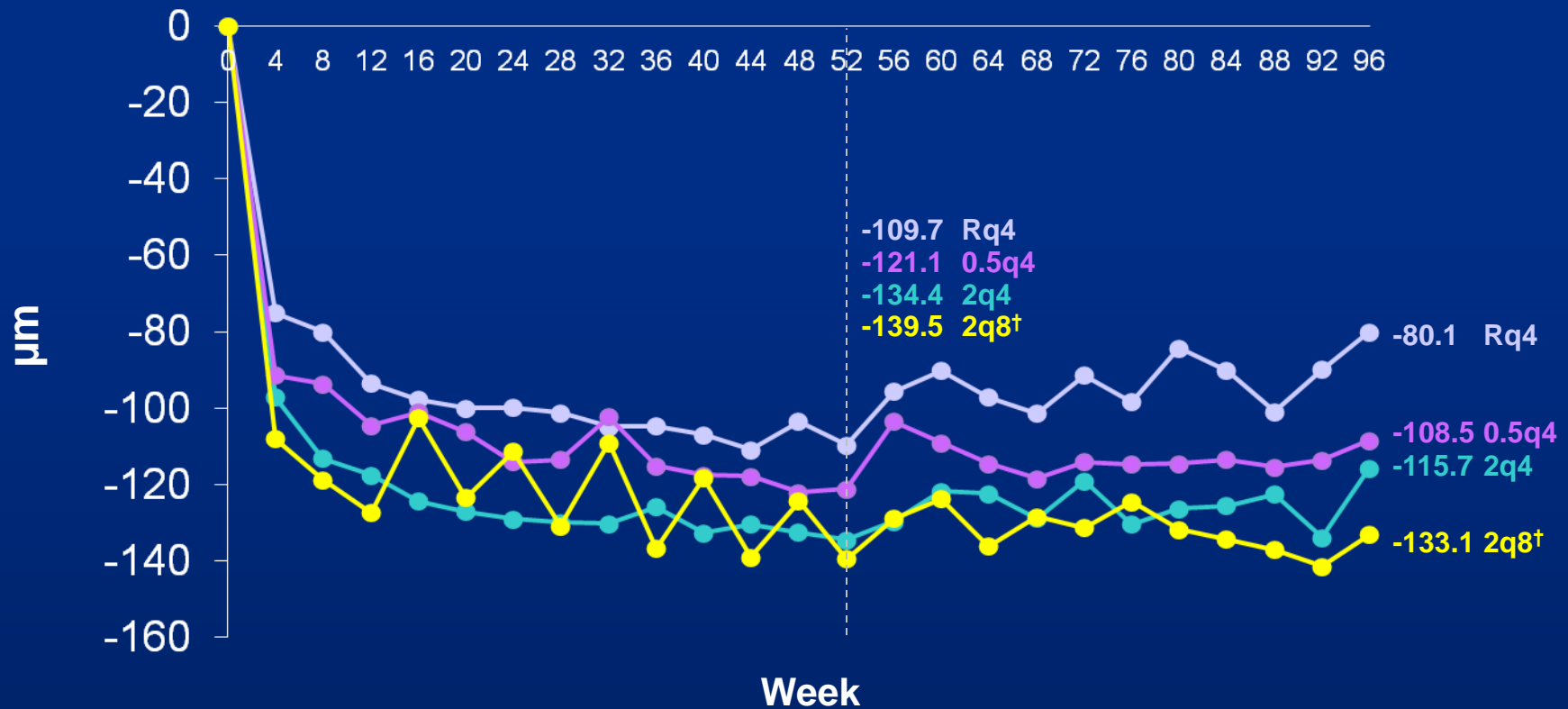
*LOCF.

†After 3 initial monthly doses.

Patients losing ≥ 5 letters between Week 52 and 96: Rq4 n=104; 2q4 n=109; 0.5q4 n=107; 2q8 n=102.

Hypothesis 1: Vision Loss Not Paralleled or Preceded by CRT Changes

Patients losing ≥ 5 letters between Week 52 and 96*



*LOCF; †After 3 initial monthly doses.

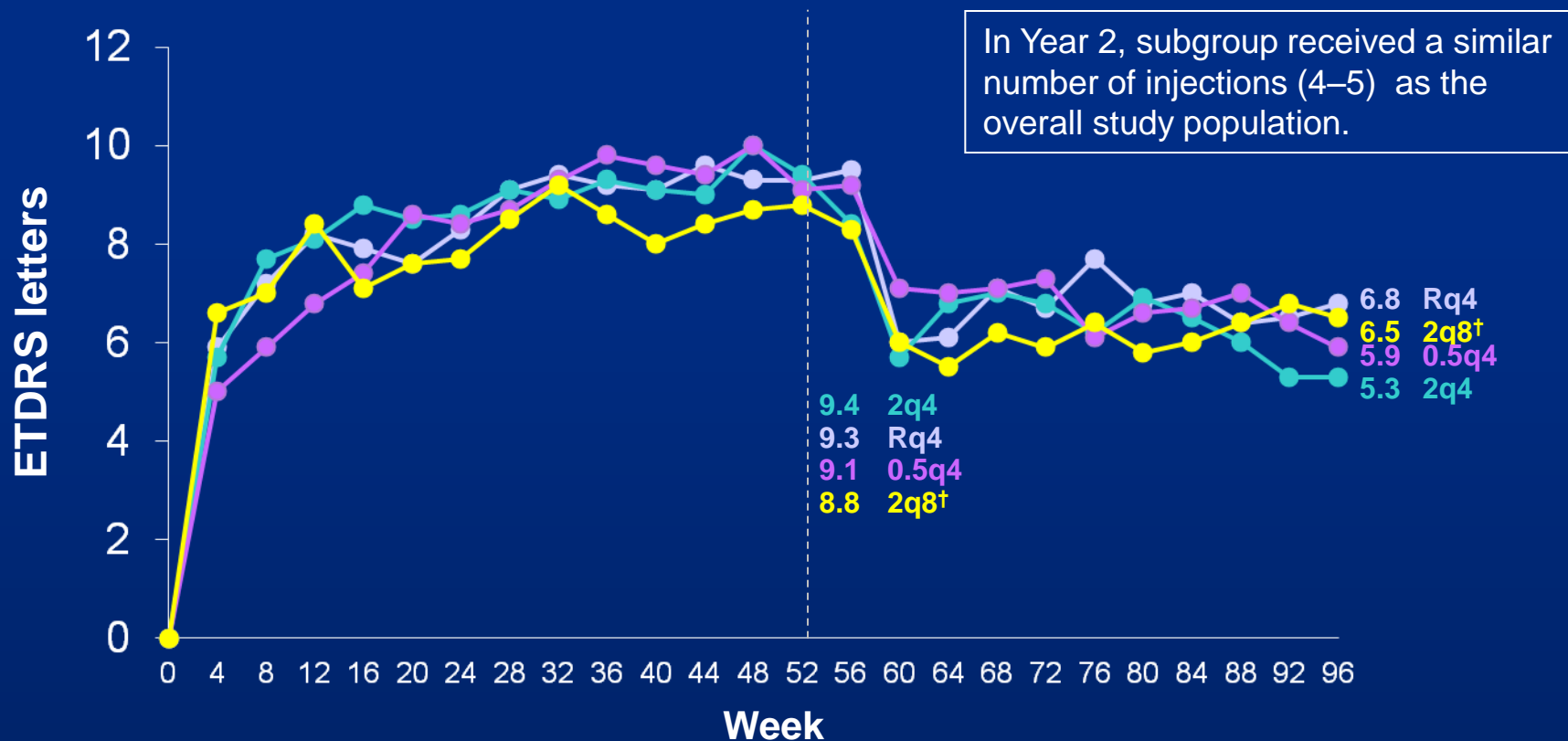
Patients losing ≥ 5 letters between Week 52 and 96: Rq4 n=104; 2q4 n=109; 0.5q4 n=107; 2q8 n=102.

VIEW 1: OCTs mandatory at baseline, Weeks 4, 12, 24, 36, and all visits from Weeks 52–96;

VIEW 2: OCTs mandatory at all visits.

Hypothesis 2: Vision Loss After Stabilization Not Reversible With Retreatment

Patients losing ≥ 5 letters between 2 consecutive visits between Week 52 and 64 with active treatment at the second visit*



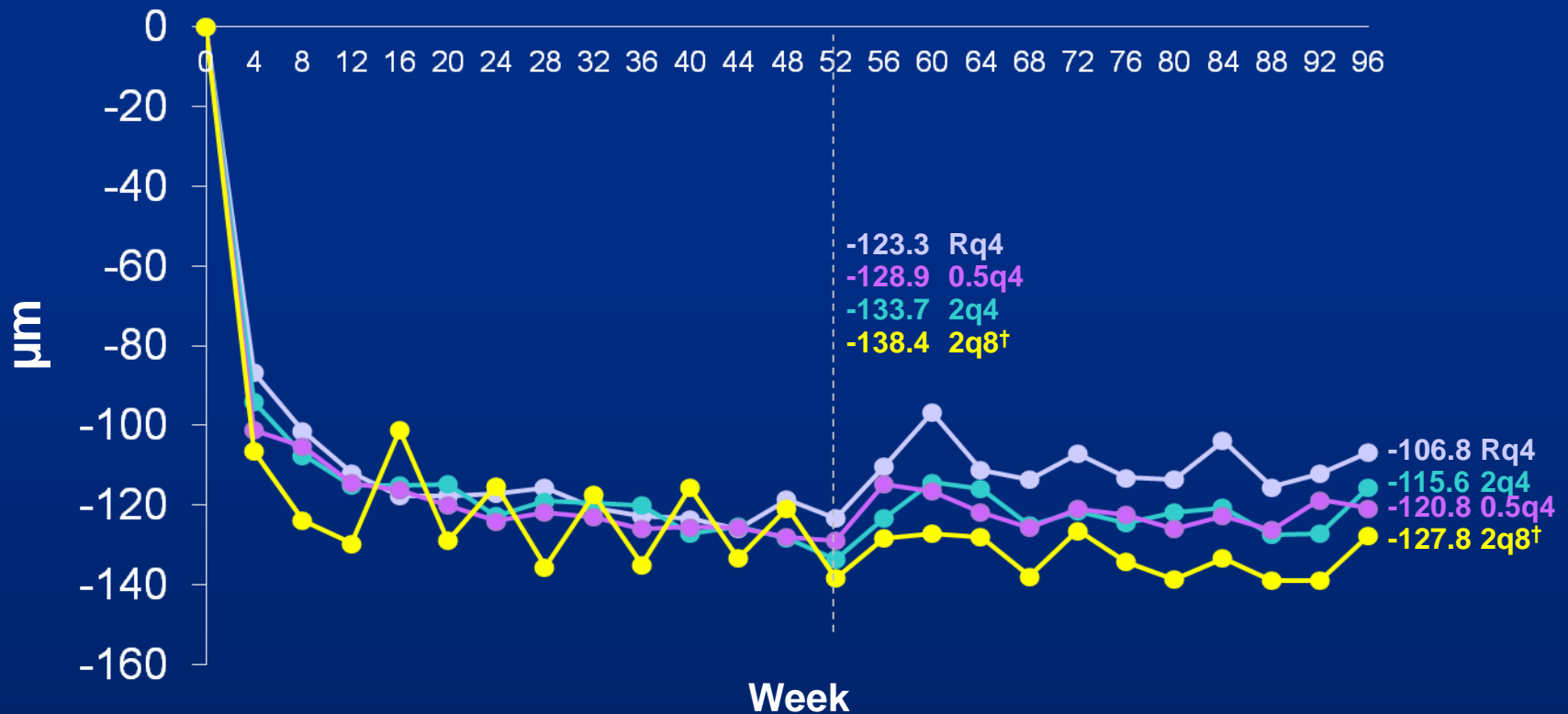
*LOCF;

†After 3 initial monthly doses.

Patients losing ≥ 5 letters between 2 consecutive visits: Rq4 n=115; 2q4 n=113; 0.5q4 n=127; 2q8 n=121.

Hypothesis 2: Vision Loss Not Paralleled Or Preceded by CRT Changes

Patients losing ≥ 5 letters between 2 consecutive visits between Week 52 and 64 with active treatment at the second visit*



*LOCF.

†After 3 initial monthly doses.

Patients losing ≥ 5 letters between 2 consecutive visits: Rq4 n=115; 2q4 n=113; 0.5q4 n=127; 2q8 n=121.

VIEW 1: OCTs mandatory at baseline, Weeks 4, 12, 24, 36, and all visits from Weeks 52–96;

VIEW 2: OCTs mandatory at all visits.

Conclusions I

- Overall visual acuity is generally maintained in Year 2; however, a slight trend for loss of vision suggests that a proactive treatment schedule results in more stable outcomes with intravitreal aflibercept or ranibizumab
- Switching treatment from an exclusively proactive treatment scheme to a treatment scheme with a reactive component leads to significant loss of visual acuity in a subgroup of patients

Conclusions I

- On a subgroup level, once lost, vision is not regained after retreatment with a reactive injection, despite stable visual acuity gains up to Week 52 under a proactive treatment schedule
- No preceding or concomitant changes of CRT were observed in analyses of patients who lost vision
- Characteristics to identify patients who may lose vision with reactive treatment regimen are unknown
- Subgroup with poor prognosis even with optimal therapy

MACULA EDEMA IN AMD

Non responders to Anti-VEGF - what to do?

- Change Anti-VEGF
- Combine with Steroids
- Combine with PDT
- Vitrectomy (?)
- Radiation therapy (?)

Photodynamic Therapy in combination with Anti-VEGF

- Verteporfin
- Activation by Laser

→ Occlusion of CNV

Side-Effects:

- Occlusion of choroidal vessels

MACULAEDEMA IN CNV

Intraocular Steroids

- Block inflammatory cascade
- Block VEGF
- Edema ↓
- Side-Effects: intraocular Pressure ↑

VITREORETINAL ADHESION IN AMD

- Higher rate of persisting posterior vitreous attachment in patients with AMD compared to those without AMD. (Weber-Krause et al 1996)
- Attachment of or only partially detached posterior vitreous in 66.6% of AMD patients. (Ondes et al 2000)
- 80% of patients with choroidal neovascularisation in AMD were found to have a central vitreoretinal adhesion. (Lambert et al 1992)
- One third of CNV-patients showed vitreomacular adhesions. (Sahni et al 2005)
- 77% of patients with exsudative AMD showed abnormalities of the vitreomacular interface. (Quaranta-El et al 2006)
- High coincidence of persistent central vitreoretinal adhesions and exsudative AMD. (Krebs et al 2007)

VITREORETINAL ADHESION IN AMD

- Contraction of epiretinal membranes and shear forces may be an additional cause of pigment epithelial detachments.
- Traction induced chronic low grade inflammation may contribute to the development of drusen or cause neovascularisation via an increase of growth factors.
- Stretching and suction induced RPE changes and stimulation of Müller cells may lead to an increase of growth factors and consecutively to neovascularisation. Dynamic vitreous traction and traction through elasticity of the posterior vitreous cortex may induce ischemic processes in the macula, again leading to an ingrowth of new vessels.
- Reduced oxygenation due to abnormal vitreous adhesion may cause ischemia and lead to neovascular processes via a breakdown of the blood retina barrier.

Epimacular Bachytherapy for neovascular Age-related Macular Degeneration

A randomized, controlled trial (CABERNET)

Conclusion: The 2 year efficacy data do not support the routine use of EMBT for treatment-naive wet AMD, despite an acceptable safety profile. Further safety review is required.

Stereotactic Radiotherapy for neovascular age-related Macular Degeneration

52-week safety and efficacy results of the INTREPID study

Purpose: To determine the safety and efficacy of low-voltage, external-beam, stereotactic radiotherapy (SRT) for patients with neovascular age-related macular degeneration (nvAMD).

Conclusions: A single dose of SRT significantly reduces ranibizumab retreatment for patients with nvAMD, with a favorable safety profile at 1 year. Whereas chronic nvAMD typically results in loss of VA over time, SRT is associated with relatively well-preserved VA over 1 year.

MACULA EDEMA IN AMD

Non responders to Anti-VEGF - what to do?

- Change Anti-VEGF
- Combine with Steroids
- Combine with PDT
- Vitrectomy (?)
- Radiation therapy (?)

ERRORS IN THE TREATMENT OF AMD

- Macularotation
- Transpupillare Thermotherapy (Induction of Chaperons)
- Radiationtherapy 8x2GY (16GY) (RAD-Study 2001)

→ Multicenter Studies!