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# Endpoints selection in registration clinical trials and the needs of real-world clinical practice with the example of anti-VEGF therapy in neovascular age-related macular degeneration

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The issues of endpoints selection for regulatory requirements and real-world clinical practice using the example of anti-VEGF therapy in neovascular age-related macular degeneration (nAMD) are discussed in the article. New technologies (optical coherent tomography) introduction are shown to change clinical practice but not regulatory requirements on the endpoints. In the same time for regulatory purpose clinical trials design is changed from superiority to non-inferiority. The changes in the approach to primary endpoint selection are not anticipated due to regulator's conservatism but there is a requirement to the comparison with best treatment alternative (i.e. same class comparator in case of anti-VEGF therapy) due to ethical reasons. To satisfy real-world clinicians need, the secondary endpoints are analyzed, but multiple testing problem appears. Statistical methods developed in recent years allow using specified comparison to be made without inflating Type I error. HAWK and HARRIER clinical trials demonstrated an example how superiority of brolucizumab over aflibercet on anatomical endpoints was reliably found.

**Keywords:** clinical trials endpoints; clinical trial ethics; multiple comparisons; hierarchical statistical testing; evaluation of anti-VEGF therapy in neovascular AMD; anatomical endpoints.

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# Особенности выбора конечных точек в регистрационных исследованиях и потребности реальной клинической практики на примере анти-VEGF-терапии неоваскулярной возрастной макулярной дегенерации сетчатки

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На примере анти-VEGF-терапии в лечении неоваскулярной возрастной макулярной дегенерации сетчатки продемонстрированы проблемы выбора конечных точек для требований регуляторных органов и реальной клинической практики. Показано, как появление новых технологий (оптической когерентной томографии) стимулирует изменение в клинической практике, однако не в конечных точках, измеряемых в исследованиях, с изменением дизайна с превосходства на не меньшую эффективность. Регуляторные органы не могут допустить смены конечной точки ввиду консерватизма, но по этическим причинам требует сравнения с наилучшим альтернативным препаратом, в случае анти-VEGF-терапии — из того же класса. Для удовлетворения потребностей клиницистов организаторы исследований проверяют также вторичные точки, но возникает проблема множественного тестирования. Разработанные в последние годы статистические методы позволяют заранее специфицировать сравнения и убрать опасность увеличения ошибки I типа. Приведен пример исследований HAWK и HARRIER, как было установлено превосходство бролуцизумаба над афлиберцептом по анатомическим конечным точкам.

**Ключевые слова:** конечные точки в клинических испытаниях; этика клинических испытаний; множественные сравнения; иерархическое статистическое тестирование; оценка анти-VEGF-терапии неоваскулярной возрастной макулярной дегенерации сетчатки; нВМД; анатомические конечные точки.

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The planning and the organization of clinical trials are labor-intensive and complicated matter, whereby being highly expensive [1]. Researchers have to take into consideration a whole bunch of aspects applied to organizers, from ethical principles of study conduct to requirements of licensing/regulating authorities to evidence level concerning efficacy and safety. One of the problems could be the choice of the clinical trial's endpoint on which its sponsor will rely determining the number of volunteers to be involved in the trial, its duration, and special aspects of statistical data processing. The understanding of how the problems facing the researchers of anti-VEGF medications which are used to treat neovascular age-related macular degeneration (nAMD) are resolved, is necessary to adequately estimate the body of evidence created for new medications.

*The aim of present article is to present* the features of new anti-VEGF molecules development and to show why the anatomical endpoints (such as fluid in the retina (intraretinal, subretinal) and that under the retinal pigment epithelium; central retinal thickness (CRT); disease activity determined by the loss in best corrected visual acuity (BCVA) of more than 5 letters and by new macular hemorrhages [2–4]) were used as secondary endpoints.

## PRESENTATION OF BASIC MATERIAL

When planning a clinical trial, the endpoints, namely variables determining efficacy and safety, are divided into primary (basic) and secondary ones. Usually, there are few primary points. They are used to calculate the required sample size for the trial and to conclude on efficacy and safety. Secondary points are used as supporting ones, and if the study protocol requires superiority or non-inferiority in efficacy (see below), regulating authorities may not give their consent to accept data where the efficacy is determined from secondary points and require to carry out one more clinical trial.

At the same time, at the development of anti-VEGF medications, researchers had to face some difficulties influencing this program. The point is that the development of anti-VEGF medications went in parallel with the development of technological methods for determination of anatomical parameters, first of all of optical coherence tomography (OCT). First registered anti-VEGF medication for nAMD treatment – pegaptanib sodium – was approved by the American Food and Drug Administration (FDA) in 2004, 11 years after the appearance of first publications about the OCT use to obtain retinal images. At that time, according to the analysis of the American National Medical Library database, there were only 17 articles published on the problem of the OCT use in nAMD (Table 1).

Obviously, the researchers of first medications had only functional evaluation methods available, namely BCVA estimation. In 2005, the results of a study were published dealing with anti-VEGF monoclonal antibody (bevacizumab) use in nAMD, which was used as off-label injections [5]. The main endpoint was certainly the visual acuity. Several clinical trials on the intravitreal bevacizumab administration were carried out [6, 7]. They were retrospective by design and did not have the degree of control on samples collection quality and procedure performance which characterizes prospective clinical studies.

In 2006, FDA licensed ranibizumab for nAMD treatment. It was done on the basis of studying its comparison to sham intravitreal injections (MARINA [8] – placebo-controlled study) and to photodynamic therapy (ANCOR [9]). Data of a phase I/II clinical trial (FOCUS [10]) were also used, where on the photodynamic therapy background, either ranibizumab or sham injections were performed. Visual acuity indicators were used as endpoints, and ranibizumab superiority was shown. It has to be stressed that the comparison was carried out with sham injections and with photodynamic therapy and not with anti-VEGF therapy (pegaptanib), because authorizations were issued with two-year interval and correspondingly, taking into consideration longer duration of registration clinical studies at the moment of ranibizumab trials, pegaptanib was not available for extensive use in the framework of multicenter registration studies. Studies carried out later to indirectly compare ranibizumab with pegaptanib allowed assuming higher ranibizumab efficacy, in spite authors pointed out to different populations included into ranibizumab trials in comparison to pegaptanib trials [11]. Nevertheless, large agencies evaluating technologies in healthcare (for example, British NICE) did not recommend using pegaptanib for nAMD treatment[1].

Taking into account the load upon the healthcare system, which was related to both with the price of

[1] NICE. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. Technology appraisal guidance. Published: 27 August 2008. www.nice.org.uk/guidance/ta155.

**Table 1.** Number of publications in PubMed database on OCT use in wet AMD (search was performed on 05/01/2021 at https://pubmed.ncbi.nlm.nih.gov with keywords AMD [TW] AND OCT [TW])

**Таблица 1.** Количество публикаций в системе PubMed об использовании ОКТ при нВМД (поиск осуществлен на https://pubmed.ncbi.nlm.nih.gov по сочетанию AMD [TW] AND OCT [TW] 05/01/2021)

| Years | Number of publications | During a year, on average |
|---|---|---|
| 1993–2004 | 17 | 1.5 |
| 2005–2011 | 269 | 38.4 |
| 2012–2020 | 987 | 109.7 |

innovation medications and with the monthly regimen of therapy, ophthalmologists began to concern themselves with increasing interval between injections without any harm to the patient. Anatomical points could be of assistance, which allowed in advance objectively evaluating worsening of the condition or slowing down of the disease progression without any substantial visual acuity loss. This increased the interest to the OCT use and to the determination of the relationship between anatomical changes and disease progression. Between 2004 and 2011, already 269 articles were published on the OCT use in nAMD. The technology itself continued to develop, becoming more accessible for clinicians.

To 2011, the clinical development program of aflibercept for nAMD treatment was accomplished. The studies continued from middle 2000s, and the endpoint was visual acuity again. A licensed effective medication ranibizumab already existed, and for ethical reasons, the comparison had to be made with it. As it is easier to prove superiority over placebo than over another effective treatment, VIEW 1 and 2 trials were based on the non-inferiority design [12]. At the non-inferiority design, there are no attempts to show that the new medication is more effective than the existing therapy or placebo. The objective is to demonstrate that it is not worse. The frontier of lower efficacy is established, which cannot be overlapped by the 95% confidence interval's lower limit [13]. Thus, a statistical warranty is given that the preparation would not approach placebo and be effective. On a formal level, it may be a little bit better or a little bit worse. "Non-inferiority" designs became popular over recent years due to the appearance of new preparations and of questions for the ethics of placebo control organization in presence of effective treatment. As a result, if in 2005 in PubMed, there were less than 100 publications of non-inferiority trials, in 2005, there were already almost 600.

At the same time, there was a growing understanding of the importance of OCT and of anatomical points measurement for evaluation of the treatment's efficacy. The number of publications concerning the OCT use in nAMD increased practically according to the exponential curve – between 2011 and 2020, 987 articles were published (about 110 in one year, or just below 10 in one month). During this period of time, the understanding of the importance of anatomical points to monitor the therapy appeared. At the same time, questionnaire data of the "2019 EURETINA Clinical Trends Survey Outcomes"[2] show that very few ophthalmologists use regular monthly injections (5% in the Western Europe and 11% – in the Eastern Europe), the rest uses PRN (*pro re nata*, that is "as needed", or under present circumstances, – 30% ophthalmologists of the Eastern Europe) or T&E (Treat and extend – 57% ophthalmologists of the Eastern Europe in the survey) regimens, in which anatomical indicators (namely, the presence of fluid) play an important role.

It became obvious for example that preservation and appearance of intraretinal/subretinal fluid (IRF/SRF)is associated with more significant visual acuity loss: loss of 15 letters in 2.8% of patients with new IRF and the same number of patients with new SRF. In total, a loss of more than 5 letters is noted in 29.6% of patients with recurrent SRF and in 33.9% – with recurrent IRF. In patients without fluid, this amount was equal to 16.6% only (ranibizumab therapy was conducted according to T&E protocol) [14].

Later on, a clinical development of one more anti-VEGF monoclonal antibody – brolucizumab took place. From the very start of the program, one could understand that in all studies the main endpoint is the visual acuity, because it was used in previous trials and is ranged by regulatory authorities as a "real" endpoint, i. e. an indicator, which measures something important for the patient. Brolucizumab studies begin with phase I/II trials, in which a search for acting dose and preliminary efficacy evaluation are performed. In the SEE study [15], there were two parts: on the first stage 0.5, 3.0 or 4.5 mg brolucizumab or 0.5 mg ranibizumab were injected, on the second – 0.5, 3.0 or 6.0 mg brolucizumab or 0.5 mg ranibizumab.

Non-inferiority in efficacy between brolucizumab 4.5 and 6.0 mg as compared to ranibizumab. CRT changes were 23 μm more (90% CI = –9.28...54.99) in the group, which received brolucizumab at a dose of 4.5 mg, and 19 μm more (90% CI = –9.0...47.8) in the group, which received 6 mg of brolucizumab, than in the ranibizumab group.

The OWL study was already only II phase trial, in which brolucizumab was compared to ranibizumab when using intravitreal injections or microinfusions [15]. There were 52 patients in total, randomized at a ratio (thus in the ranibizumab group few patients happened to be included – 12 only). Brolucizumab treatment was performed as: 1.2 mg/10 mcl injection; 0.6 mg/10 mcl injection; .0 mg /8.3 mcl microinfusion; 0.5 mg/8.3 mcl microinfusion. Ranibizumab: intravitreal injection 0.5 mg/50 mcl. In both groups a positive treatment result was noted.

One more II phase study was accomplished – OSPREY [16], it was a 56-week study comparing the efficacy of 6 mg brolucizumab and 2 mg aflibercept intravitreal injections. There were 89 participants in total receiving a therapy following the pattern: 3 injection intervals every 4 weeks, then every 8 weeks, and later on every 12 weeks in the brolucizumab group and 8 weeks in the aflibercept group. The so-called posthoc-analysis included the evaluation of CRT changes and of SRF/IRF presence. CRT changes on Week 12 were –197 and –189 μm, on Week 40 – –198 and –178 μm, correspondingly. The number of eyes with SRF/IRF was 9.3 и 20.9% on Week 12 and 14.6 and 32.5% on Week 40 in brolucizumab and aflibercept

[2] The Interim 2019 EURETINA Clinical Trends Survey Outcomes // The great fluid debate – Retina Today. https://retinatoday.com/pdfs/1219_insert4.pdf. Access regimen: 27.11.2020.

groups. Obviously, one could predict, that brolucisumab had an edge over aflibercept concerning anatomical points. But as mentioned before, regulatory authorities would not accept a transition to a new endpoint.

There is also one more problem, encountered when analyzing several groups in studies, – this is the problem of multiple comparisons [17]. At its simplest, its description looks like following: every time, when we perform group comparisons, we decline the zero hypotheses (about the nondiversity) at 5% level (0.05). Correspondingly, in 5% of studies, comparing two equally effective interventions, there is a risk to acknowledge superiority in one of the groups, although this is not true. If an analysis of 3 points is performed, the probability of false conclusion would be already not 5%, but 14.3%. This is why the multiplicity of comparison has to be taken into account somehow. The most simple could be the Bonferroni method, which simply lowers the level of significance to a number of comparisons – if they are 5. The limit level would be equal to 1%. Therefore, to assure the possibility of significant efficacy comparison based on changes of anatomical points, the protocol was very carefully adjusted from the statistical point of view.

And now some words about registration studies HAWK and HARRIER [18]. By design, it were two-year multicenter randomized double-blind trials of "non-inferior efficacy" with active control. As a control анти-VEGF medication, aflibercept was chosen. The HAWK trial: 1082 nAMD patients were randomized as 1 : 1 : 1 into three groups, receiving brolucizumab at a dose of 3 mg, brolucizumab – 6 mg or aflibercept – 2 mg as intravitreal injections. The HARRIER trial: 743 patients were randomized as 1 : 1 into two groups, receiving intravitreal injections of brolucizumab at a dose of 6 mg or aflibercept at a dose of 2 mg. HAWK was carried out in the Northern America, Latin America, Japan, Australia, New Zealand, and Israel. HARRIER – in EC countries, the Middle East, Asia, and Russia.

The primary outcome was the change of best corrected visual acuity (BCVA) from the study start up to Week 48. It has to be noted that the duration of the study was 96 weeks, and during the whole period, the follow-up and treatment of patients continued, but there couldn't be any new primary endpoint at the late stages of the trial. As patients of different age groups and with different visual acuity, the analysis included correction with a statistical model and calculation of BCVA difference between Week 48 and baseline data. Notably, the statistical model adjusted differences related to different baseline visual acuity and age (so-called predicted marginal means, or least-squares means [LSMEANS]). As non-inferiority margin, 4 signs were chosen[3]. The results appeared as follows: HAWK –0.16 (95% CI [–2.13; 1.80]) (brolucizumab at a dose of 6 mg in comparison with aflibercept), HARRIER –0.70 (95% CI [–2.39; 1.00]). Lowest values of 95% confidence interval were higher than the non-inferiority margin, and this means that the primary goal of the study – obtaining non-inferiority evidences – was reached. It is important because in such complex designs, a hierarchical testing is used, and if the results on primary outcome were not positive, the following testing would be inconclusive. Such tough approach to the evaluation of clinical study results allows creating models, which allow to answer the question: what if in clinical study brolucizumab would be compared not with active control, but with placebo? With this in mind, H. Agostino, et al. [19] carried out a comparison of HAWK/HARRIER data with data of model effect on placebo. The model was created based on ANCOR, MARINA, PIER, EXCITE data и validated on HARBOR study data [20]. It was taken into account that age and baseline visual acuity play a prognostic role. According to the model, the effect from brolucizumab use versus placebo was equal to +22 signs by Week 48, and +28 signs by Week 96.

The main objective of the present study was to show, want efforts were under way to ensure the level of evidence of comparing anatomical points by brolucizumab and aflibercept therapy. Based on results of prervious studies on brolucizumab efficacy, following indicators were chosen as main indices of testing: CRT change, absence of IRF/SRF, and disease activity. These three indicators had to be taken into consideration to preserve on the predetermined level the type 1 errors, or as they say to prevent "false discoveries". This was made only in HAWK trial (statistical analysis in HAWK was created taking into account HARRIER [18]). The authors of the statistical analysis plan in the study decided to choose the method of type 1 error (α-error) between indices level separation (global test for superiority). Because they intended to use single tail tests, they had to divide the error level of 2.5% (0.025, or conventional two-tailed significance level of 0.05, divided into 2). The authors decided to divide the error level as follows: CRT change – 0.005; absence of IRF/SRF – 0.01; disease activity – 0.01. It has to be noted that the protocol authors considered the disease activity and absence of IRF/SRF more important than CRT changes, because to prove the superiority in this point was more difficult. Further on, multiple hierarchal tests were done, as for example for CRT changes:

1) brolucizumab at a dose of 6 mg vs aflibercept at Week 16;

2) brolucizumab at a dose of 6 mg vs aflibercept at Week 48;

3) brolucizumab at a dose of 6 mg vs aflibercept for median of Weeks 36, 40, 44, 48;

4) brolucizumab at a dose of 3 mg vs aflibercept at Week 16;

5) brolucizumab at a dose of 3 mg vs aflibercept at Week 48;

[3] Calculations of the lower efficacy limit were performed according to data on aflibercept efficacy in comparison with ranbizumab, and of ranibizumab in comparison with placebo provided no less than 50% of the effect in comparison with placebo was preserved.

6) brolucizumab at a dose of 3 mg vs aflibercept for median of Weeks 36, 40, 44, 48.

Here 6 hypotheses are tested sequentially, from 1st to 6th, at that if even one hypothesis in the sequence happens to be accepted (the *p* value happens to be higher than the aforesaid limit), further hypotheses are not tested (Table 2), this approach has a name of gatekeeping method [21].

Then, reliable information was obtained on the superiority of brolucizumab therapy at a dose of 6 mg by anatomical endpoints, first of all, by IRF/SRF presence and CRT, because the evaluation for the disease activity estimation was performed only on Week 16 due to the change of disease activity determination at more advanced terms. Attention must be paid to extremely low *p* values in HAWK study, which, taking in mind the preliminary formulation in the protocol protects against false discoveries. It is interesting that in the publication on the results of 96-weeks trials HAWK и HARRIER [24], the authors found it necessary to point out that *p* estimations are descriptive (because the analysis on Week 96 was not foreseen), however data on anatomical points were also highly significant and spoke well for brolucizumab.

## CONCLUSION

The development of science and technological basis of medicine leads to the appearance of new markers to monitor and modify the therapy. However easily understandable conservatism of the regulatory system in combination with

**Table 2.** Evaluation of superiority hypothesis in HAWK and HARRIER trials (supplementary materials to article by P.U. Dugel, et al [18])
**Таблица 2.** Оценка гипотез превосходства в исследованиях HAWK и HARRIER (дополнительные материалы к статье P.U. Dugel и соавт. [18])

| Indicator | Endpoint evaluation at a period | Brolucizumab dose, mg | Local significance level | *p* for superiority (single tail test) | Significance according to testing procedure |
|---|---|---|---|---|---|
| CRT (HAWK) | Week 16 | 6 | .005 | <.001 | Yes |
| | Week 48 | 6 | .005 | .001 | Yes |
| | Weeks 36–48 | 6 | .005 | .008 | No, *p* > .005 |
| | Week 16 | 3 | .005 | .016 | Previous hypothesis was not rejected |
| | Week 48 | 3 | .005 | .008 | Previous hypothesis was not rejected |
| | Weeks 36–48 | 3 | .005 | .018 | Previous hypothesis was not rejected |
| CRT (HARRIER) | Week 16 | 6 | – | <.001 | NA |
| | Week 48 | 6 | – | <.001 | NA |
| | Weeks 36–48 | 6 | – | <.001 | NA |
| Presence of IRF/SRF (HAWK) | Week 16 | 6 | .01 | <.001 | Yes |
| | Week 48 | 6 | .01 | <.001 | Yes |
| | Weeks 36–48 | 6 | .01 | .001 | Yes |
| | Week 16 | 3 | .01 | .003 | Yes |
| | Week 48 | 3 | .01 | .002 | Yes |
| | Weeks 36–48 | 3 | .01 | .057 | No, *p* > .01 |
| Presence of IRF/SRF (HARRIER) | Week 16 | 6 | – | <.001 | NA |
| | Week 48 | 6 | – | <.001 | NA |
| | Weeks 36–48 | 6 | – | <.001 | NA |
| Presence of active disease (HAWK) | Week 16 | 6 | .01 | .001 | Yes |
| | Week 16 | 3 | .01 | .033 | No, *p* > .01 |
| Presence of active disease (HARRIER) | Week 16 | 6 | – | .002 | NA |

*Note.* CRT – central retinal thickness, IRF/SRF – intraretinal/subretinal fluid.

ethical demands to interventions in the control group creates a situation when such markers cannot be primary indicators of efficacy. In such conditions, a careful planning of the statistical analysis allows to avoid the danger of "false discoveries" and to affirm that the revealed superiority is true. However this does not bother to perform post-registration trials later, which would allow receiving additional information upon brolucizumab therapy in the group of patients with a non-optimal nAMD control by anatomical points (clinicaltrials.gov identificator NCT04264819).

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