

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Chin C. Koerner
Tel: 301-468-5602
Fax: 301-468-5614
email address: chin.koerner@pharma.novartis.com

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Division of Dockets Management (HFA- 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Novartis Comments on FDA Critical Path Initiative
Docket No 2004-N-0181

Dear Sir/Madame:

Novartis Pharmaceuticals corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group Companies employ more than 78,000 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

Novartis and the FDA share a mutual interest in bringing safe and effective products to patients. As one of the world's largest pharmaceutical companies, Novartis commits extensive resources to research and applauds FDA's efforts to stimulate innovation through the Critical Path Initiative.

While the publication "Challenge and Opportunity on the Critical Path to New Medical Products" is excellent in outlining an overarching strategy, specific solutions will require specific actions by both industry and FDA.

We offer the following suggestions for your consideration. As Novartis has considerable experience in these areas, we look forward to working with FDA to advance these topics onto the "Opportunity List".

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I. Alternative Methods for Evaluation of Efficacy and Safety

1. Turning Biomarkers into Surrogate Markers

The following proposals are based on published evidence correlating specific biomarkers and relevant clinical endpoints. (To facilitate your review, a list of references is included.) The use of such biomarkers as surrogates to the clinical endpoints would result in significant reduction of time and resources required for drug development, thus encouraging research that will ultimately benefit patients. Importantly, since changes in biomarkers often occur before and are predictive of disease complications, therapy, in some instances, could be started as an earlier stage in the disease process to delay or prevent such complications.

A development/validation plan could include one phase 3 outcomes study with currently accepted endpoints AND surrogate endpoint(s) and a second surrogate endpoint – only confirmatory study to support approval. A phase 4 study with currently accepted endpoints could then be conducted as further confirmation of efficacy.

1.1 Microalbuminuria (MA) as endpoint for diabetic nephropathy:

There is need for predictive earlier biomarkers of initial impairment or worsening of renal function. If, therapeutic goal is to prevent or delay nephropathy, complete and sustained disappearance of MA is suggested as an acceptable endpoint for early renal disease when renal function is still normal.

For later stages of renal disease, more work is needed to show correlation between MA and creatinine including a clinically relevant decrease in creatinine or showing a clear effect on reducing the slope of the change in creatinine vs. time. Current endpoint for diabetic renal dysfunction is doubling of serum creatinine.

References

1. Dineen SF, Gerstein HC; Arch Int Med 157: 1413-1418, 1997
2. Andersen S, Brochner-Mortensen J, Parving HH; Diabetes Care: 26;3296-3302, 2003
3. Gaede P, Vedel P, Parving HH; Lancet: 353; 617-622, 1999
4. Ahmed J, Siddiqui MA, Ahmad H; Diabetes Care: 15676-1581, 1997
5. Hope/Micro-Hope Investigators; Lancet: 355; 253-259

1.2 Two-year fracture Data instead of three-year fracture data in Osteoporosis BMD + bone quality assessments instead of fracture data in Osteoporosis

There is medical agreement that BMD is important for making the diagnosis of osteoporosis, evaluating fracture risk, making decisions regarding which patients should initiate therapy, and assessment of dose selection in clinical development. While BMD alone explains a proportion of anti-fracture effects, BMD response to therapy overall correlates with vertebral and non-vertebral fracture reduction, especially for bisphosphonates.

For agents that produce normal bone quality (preclinical), 1-2 years appears adequate to demonstrate anti-fracture benefit that is sustained during longer observation periods.

We suggest that BMD and bone quality assessments may be suitable endpoints for efficacy in osteoporosis. Additionally, two year fracture data instead of three year fracture data should be considered as a clinically meaningful endpoint.

References

1. Harris ST, et al.; *J Am Med Assoc (JAMA)* 282: 1344-52, 1999
2. Black DM, et al.; *J Clin Endocrinol Metab* 85: 4118-24, 2000
3. Wasnich RD, Miller PD.; *J Clin Endocrinol Metab* 85:231-6, 2000
4. Cummings SR, et al.; *Am J Med* 112:281-289, 2002
5. Hochberg M, et al.; *J Clin Endocrinol Metab* 87:1586-1592, 2002

1.3 Time with intragastric pH >4 instead of endoscopy in healing of erosive esophagitis (or symptomatic GERD or peptic ulcer)

Gastric acid inhibition is routinely evaluated by 24-hour intra-gastric pH monitoring. Time with pH4 correlates well with healing of acid related diseases. There is suggestion from modeling and meta-analysis that intra-gastric pH monitoring of a dose of an acid inhibitor can be inferred to produce a certain rate of healing of acid related disorders. Such an approach would be more time and cost efficient and less invasive than the current endoscopy at 6 weeks post treatment endpoint.

References

1. *Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression?* DW Burget, S G Chiverton and R H Hunt; *Gastroenterology* Volume 99: August, 1990
2. *Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis.* N. Chiba, C J De Gara, J M Wilkinson and R H Hunt; *Gastroenterology* Volume 112: June, 1997

II. Seamless Adaptive Clinical Trial Designs: An approach to allow learning from information accrued during the trial in a confirmatory framework and combining phase IIb and III trials in one single trial.

The use of information gathered in the learning stage (IIb) of the trial to adapt the design for the next, confirmatory stage (III) and to contribute evidence to the overall conclusions leads to overall fewer patients as compared to the usual consecutive phase IIb / III paradigm.

The seamless transition from first to second stage will shorten overall development time and long term safety data from patients on the right dose becomes available earlier (extension of phase IIb patients)

Adaptive designs can be used as a substitute for classical fixed designs within all phases of development and are necessary if a trial that combines phases is envisaged. They help to increase the probability of choosing the right dose /population without increase of sample size and allow treating fewer patients on suboptimal treatment strategies or patients with characteristics not favorable for a treatment response.

Seamless designs (that are in nature also adaptive) lead to a reduction of development time by moving the planning and design period between phase IIb and III before phase IIb (and hence remove it from the critical path). They also have the potential to reduce the patient numbers necessary by combining evidence gathered in the first stage with that of subsequent stage(s) for hypothesis testing. Should the results after the learning stages not support any of the foreseen design options for phase III; an adaptive trial design allows stopping the trial.

1. Selection of appropriate patient sub-group and confirmation of benefit in one seamless phase II/III trial by a 2-stage seamless adaptive design

Stage 1: Sub-group selection (options: sub-group or all-patients) or futility decision based e.g. on Bayesian methods. The sub-groups considered are defined upfront, based on evidence external to the trial, e.g. on molecular characteristics of tumor cells or on genomic and protein characteristics. The operating characteristics of design and decision strategies for sub-group selection are described a-priori via simulations

Stage 2: Achieve confirmation of treatment benefit while maintaining integrity (false positive rate controlled) of the trial.

The methodology to combine the evidence from first and second stage is frequentist in nature. The specification of how information will be combined would not depend on the information accrued in stage 1. The decision or selection strategies after the first stage need not be stated beforehand and can make use of Bayesian tools.

2. Selection of appropriate dose(s) and confirmation of benefit in one seamless phase II/III trial

In a case where there is just a few dosages to be tested (e.g. use of a drug in a new indication where there is sufficient information regarding safety, within the intended dose range) a 3-stage seamless adaptive design could be chosen to achieve the goals of phases IIb and III simultaneously.

Stage 1: Dropping ineffective dose(s) or use of futility criterion to stop trial early

Stage 2: Selection of best dose(s)

Stage 3: Confirm treatment benefit while integrating pertinent information from stages 1 and 2 while maintaining integrity of the trial, using appropriate methodology to account for the multiplicity of hypotheses in the first 2 stages.

Reference

Hommel G., *Adaptive Modifications of Hypotheses After an Interim analysis*, *Biometrical Journal* 2001, pages 581-589

In closing, Novartis Pharmaceuticals is thankful for the opportunity to provide comment and hope this response will assist in the development of the "Opportunity List" under the Critical Path Initiative.

Sincerely,

A handwritten signature in black ink that reads "Chin Koerner". The signature is written in a cursive, flowing style.

Chin Koerner
Executive Director
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation