AstraZeneca

Date: OCT 3 1 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: Docket Number 2005N-0311
Response to FDA Call for Comments
Critical Path Initiative; Developing Prevention Therapies; Planning of Workshop

Dear Sir or Madam:

Reference is made to the August 3, 2005 Federal Register notice announcing the request for comments on the proposed scope of the planned workshop for Developing Prevention Therapies.

AstraZeneca has reviewed this proposal and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Greg Taylor, Regulatory Affairs Manager, at (302) 886-1216.

Sincerely,

Barry Sickels, Executive Director
Regulatory Affairs
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Enclosure

Docket No. 2005N-0133, Critical Path Initiative; Developing Prevention Therapies; Planning of Workshop

AstraZeneca shares in the belief that prevention of illness is an important goal and welcomes and supports the FDA initiative to explore approaches and potential obstacles to developing drugs, disease biomarkers, medical devices, and vaccines to prevent or reduce the risk of illness. AstraZeneca appreciates the opportunity to comment on the proposed scope of the workshop and has done so herein. In addition, AstraZeneca would welcome the opportunity to present at the workshop, or recommend speakers, as the scope is finalized.

AstraZeneca supports the proposed 2-day format with the first day devoted to identifying hurdles and challenges in designing and implementing chemoprevention studies from a broad perspective, and the second day devoted to breakout-sessions focusing on specific diseases.

The questions proposed for day 1 seem appropriate for tackling the issue from a broad perspective. For day 2, AstraZeneca would like to suggest inclusion of the following topics.

Alzheimer's Disease - Prevention/reduction of prevalence
Alzheimer's Disease (AD) is a progressive neurodegenerative disease and the leading cause of dementia with a prevalence of 14 million patients. The condition is expected to have an epidemic growth (30 million by 2050) due to an aging population. Currently available treatment of AD is restricted to drugs with symptomatic effect only. There is a large unmet medical need for drugs that prevent, halt or delay the disease progression. A great number of initiatives exploring possibilities to influence the underlying pathology of AD are ongoing within academia and the innovative pharmaceutical industry.

Currently there seems to be no official consensus on key issues relating to development of drugs to prevent, halt or delay AD. We suggest AD to be one of the specific diseases discussed in the workshop planned. The term Mild Cognitive Impairment (MCI) is generally used to refer to a transitional zone between normal cognitive functions and clinically manifest AD. A variety of criteria for defining cognitive impairment have been utilized, but they are essentially common in that they (i) refer to non demented persons with cognitive deficits, and (ii) represent a clinical syndrome that can be utilized to classify persons who do not fulfill a diagnosis of dementia, but who have a high risk of progressing to a dementia disorder. A specific subtype of MCI, amnestic MCI, has been demonstrated to lead to a higher conversion rate to AD. The definition of amnestic MCI refers to subjects presenting with only memory impairment, where the non-memory domains of cognition are intact.

The discussion is suggested to cover:

- Selection of target population including aspects of diagnostic criteria, sensitivity and specificity as well as regulatory acceptance.
    - Patients with early AD
    - MCI
    - Specific subtypes of MCI, e.g. amnestic MCI
    - AAMI

- How to differentiate symptomatic effects from impact on underlying disease pathology in terms of specific study designs, e.g. randomized start design or withdrawal design. Could the use of specific biomarkers be helpful to differentiate between symptomatic effect and an effect on the underlying pathology?
- What kind of biomarkers would typically support a preventive or disease modifying effect of a drug? Would one biomarker be sufficient or would it be necessary to combine anatomical, functional and mechanistic biomarkers?
- What magnitude of effect would be considered meaningful?
- Risk/benefit balance considering treating a population with limited symptoms of the underlying disease vs. preventing/halting a devastating disease. What would be acceptable?
- Study design
    - Duration of studies.
    - Dose finding strategy? How would this be performed with drugs without any direct symptomatic effects, where the effect might be demonstrated after 1-2 years of treatment? Would an effect on biomarkers be acceptable.
    - Would it be appropriate to include patients in early stages of AD who are treated with current drugs considered to have a symptomatic effect only?
    - How to handle patients if symptomatic treatment is initiated during the course of the study.
    - Enrichment studies, e.g. subpopulations of MCI more likely to develop AD, subjects with a family history of AD, ApoE4 carriers etc.
- Outcome measures
    - Cognitive scales suitable and acceptable for early stages of dementia taking into account limitations with floor and ceiling effects of the currently recommended ADAS-Cog.
    - Which global scales would be applicable with study durations greater than one year.
    - Are there instruments capturing Activities of Daily Living with sensitivity also in very early stages of AD?

Parkinson's Disease – Prevent/Halt/Delay disease progression

Parkinson's Disease (PD) is a progressive neurodegenerative disease characterized by motor symptoms such as tremor, bradykinesia, muscle rigidity, gait dysfunction and postural instability. It is one of the most common chronic neurodegenerative diseases in the elderly with a prevalence of 1-2 per 1000 population, and the number of patients is expected to grow by 1-3 % per year due to an aging population. Currently available treatment of PD is restricted to drugs mainly with symptomatic effect. There is a large unmet medical need for drugs that prevent, halt or delay the disease progression. A great number of initiatives exploring possibilities to influence the underlying pathology of PD are ongoing within academia and the innovative pharmaceutical industry. Currently there seems to be no official consensus on key issues relating to development of drugs to prevent, halt or delay PD. We suggest PD to be one of the specific diseases discussed in the workshop planned.

The discussion is suggested to cover:

- Selection of population including aspects of diagnostic criteria, sensitivity and specificity as well as regulatory acceptance.
    - Patients with early PD, drug naïve
    - Patients with early PD, on treatment
    - Patients with advanced PD
- How to differentiate symptomatic effects from impact on underlying disease pathology in terms of specific study designs, e.g. randomized start design (delayed start design) or withdrawal design. Could the use of specific biomarkers be helpful to differentiate between symptomatic effect and an effect on the underlying pathology?
- What kind of biomarkers would typically support a preventive or disease modifying effect of a drug? Would one biomarker be sufficient or would it be necessary to combine anatomical, functional and mechanistic biomarkers?
- What magnitude of effect would be considered meaningful (when using clinical scales, biomarkers)?
- Study design
    - Duration of studies.
    - No of patients.
    - Dose finding strategy? How would this be performed with drugs with/without any direct symptomatic effects, where the protective effect might be demonstrated after 1-2 years of treatment? Would an effect on biomarkers be acceptable?
    - How to handle patients if symptomatic treatment is initiated/modified during the course of the study.
- Outcome measures
    - UPDRS – Use all parts? Only part II and III?
    - Time to added symptomatic therapy in drug naïve? Or number of patients requiring add-on therapy during study period?
    - Reduction in concomitant therapy?
    - Time to appearance/reduction of levodopa induced motor fluctuation? Reduction in total daily "off time"?
    - Validated scales for hyperkinesia?
    - Use of diaries?
    - Are there instruments capturing Activities of Daily Living with reasonable sensitivity? Also in very early stages of PD?
    - Cognitive scales suitable and acceptable for measure of dementia?
    - Biomarkers, which would be the most suitable?
        - Imaging : PET (which ligand?)? SPECT (which ligand?)? MRI?
        - Others

Osteoarthritis

Osteoarthritis is a chronic disease, which progresses in severity with time. When patients initially present with osteoarthritis they are relatively healthy hence intervention at the early to mid stage of the disease is aimed at reducing the risk of disease progression. Thus the challenges of disease modification of osteoarthritis are similar to those associated with the

prevention of cardiovascular disease. Currently the following options area available for identifying populations at risk from osteoarthritis: genetics, environmental, biomarkers (both biochemical and imaging e.g. MRI). Given the therapy will be chronic administration over several years, AstraZeneca would welcome the opportunity to discuss the level of risk acceptable for a candidate therapy intended for disease prevention/modification of osteoarthritis. The current regulatory endpoints for demonstrating an effect on structural progression necessitate trials of up to 2 years in duration to demonstrate an effect that can be measured radiographically. If biomarkers, either biochemical or imaging (e.g. MRI), were accepted for registration the duration of the clinical trails of a disease modifying agent could be reduced to 12 months or less. Currently the obstacles to developing compounds for chemoprevention are the duration of the clinical trials and the lack of consistency in regulatory guidance, for osteoarthritis, in the major ICH regions. The challenges from the patient perspective include acceptable duration for an observed effect on patient benefit, acceptable risk/benefit ratio for a chronically administered therapy.

Asthma

The genetics of asthma are complex but children of parents who are atopic and/or have a past medical history of asthma are at high risk of developing asthma. We are beginning to identify both genetic and cellular functional differences to enable diagnosis of at risk children. Factors within the environment that contribute to "triggering" development of the asthma phenotype include: timing of infant respiratory infections, "ultra" hygienic homes, and parental smoking. The objective of a chemoprevention treatment would be a therapy that carries the expectation that a child at high risk will not enter a lifetime of asthma, in other words prevent the acquisition of the asthma phenotype. These treatments are directed to inhibit or block the impacts of environmental factors preventing the change to an aberrant immune phenotype. The goal of treatment would be to enable an "at risk asthmatic" child to avoid a lifetime of disease.

To test for this requires the development of alternative measures of asthma and discussions could focus here. Under most circumstances, efficacy would take a lifetime to demonstrate. However, allied to the adult remission therapy, it will be necessary to use tests and measurements of the normal immune phenotype compared with the asthma phenotype. These tests will need to be validated with establishment of the relationship between immune phenotypes and disease state. There is a need to understand the stability of normal immune phenotypes in the face of environmental "challenges." Success in this area of medicine would result in a paradigm shift in asthma therapy. We anticipate that secondary prevention (remission) would be possible with the same treatments in adolescent and adult asthmatics.

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is one of the four most common causes of death worldwide, three of which are causally linked to cigarette smoking. It is characterized by more rapid annual loss of lung function and more frequent exacerbations (upper respiratory infections triggering temporary loss of lung function) than in the normal population. The other two diseases caused by smoking are lung cancer and cardiovascular disease. Potentially similar pathobiological mechanisms are involved in these diseases, as they share a similar

dose relationship to smoking and occur in later years of life. Indeed the failure to restore a normal risk profile on quitting after the age of 45 years indicates that age has a major role in withstanding the chronic impact of tobacco smoke exposure. Restoration of function on quitting is seen primarily in the young. COPD patients after the age of 55 show very limited improvement of their lung function on quitting.

Cessation of smoking can only be seen as part of the options for prevention of COPD. Patients can be expected to quit smoking in increasing numbers, assisted by more effective therapies for "craving." However, those patients of middle years and older will not gain greatly in health. AstraZeneca considers discussion around questions similar to those included in the breakout sessions of the proposed agenda appropriate for this topic as well and an important step in other new treatment options.

Apolipoproteins as markers of CV Risk

It is noted that cardiovascular prevention issues are currently included in the scope of the agenda, and we would suggest a specific discussion of apolipoproteins as a new, strong marker of CV risk. Recent intervention studies (AfCAPS/Texcaps and INTERHEART) have indicated that ApoB/ApoA-1 ratio is one of the best lipid related predictors for future myocardial infarctions. The rationale for using the ApoB/ApoA-I ratio is based on the roles of ApoB and ApoA-I in the transportation of the different lipoprotein particles. Thus, the value of the ApoB/ApoA-I ratio is a summary index of risk which contains information from all ApoB-containing and potentially atherogenic lipoproteins, and the athero-protective ApoA- I containing HDL particles.

The ApoB/ApoA-I ratio has been shown to predict fatal myocardial infarction in more than 2,000 males and females in the AMORIS study (Walldius et al, 2001, 2002). The ratio was a stronger predictor than total cholesterol, TG, LDL-C, non-HDL-C and any other lipid ratios such as TC/HDL-C and LDL-C/HDL-C.

These results were verified and extended to a multi-ethnic population in the recent INTERHEART study. This case control study, comprising more than 15,000 controls, showed that ApoB/ApoA-I ratio was the strongest risk predictor for myocardial infarction independent of smoking, hypertension, diabetes, abdominal obesity, psychosocial stress, exercise, alcohol and vitamin intake. In summary, the results from these studies indicate that ApoB/ApoA-I is a valid surrogate marker of cardiovascular risk.

Again, AstraZeneca thanks the Agency the for the opportunity to comment and for taking the initiative to arrange for a workshop in this important area, and we look forward to collaborating with the Agency and others at the workshop.