Dear Committee Member,

Thank you for agreeing to attend this meeting. We greatly appreciate your efforts to help inform the agency. We know that it is a significant effort to review the background documents and attend such meetings when we are all so busy, so thank you for taking the time.

This meeting is being held to review the efficacy and safety of leflunomide in the context of the universe of available therapies to treat the fundamental biologic processes involved in rheumatoid arthritis, which unfortunately despite significant progress remains an incurable disease.

The sponsor of NDA 20-905 for leflunomide has recently submitted an efficacy supplement for improvement in physical function. In addition, safety concerns particularly related to hepatotoxicity have been raised based on post marketing reports of acute liver failure. The division has attempted to rigorously assess this safety concern and requests committee input regarding the overall benefit to risk ratio of leflunomide based on these assessments. Attached are the relevant divisional reviews, internal agency consultations and the reports provided by external expert consultants.

The RA guidance document (Final, 1998) identifies an indication for improvement in disability based on an adequate two year data base to support such a claim. Previous review of attempts to analyze two year long placebo controlled blinded studies have identified a major difficulty in maintaining robust active therapy and placebo control over such a long duration. These data will be presented at the advisory committee meeting. In addition, the concept of disability has undergone evolution in the context of medical and legal definitions while the clinical meaning of the Health Assessment Questionnaire (HAQ) and its derivatives as patient reported outcomes of physical function have been further studied and evidenced in the medical literature.

The division is now considering whether the term "physical function" rather than "disability" is the best clinically relevant way to describe the information conveyed by the results of studies using the patient reported outcomes in the HAQ as the study instrument. Dr. James Fries will provide background discussion of this instrument. The committee is asked to consider the adequacy of shorter duration placebo and or active (6-12 months) controlled studies in conjunction with subsequent longer-term active controlled study for evidencing durability of effect for improvement in HAQ as an endpoint to describe improvements in physical function. Data submitted and reviewed by the division will be provided in the sponsor briefing document.