## b. Induction Phase and Maintenance Phase for Clinical Trials on SLE

A review article of various clinical trials on SLE referred to the use of drugs, in various combinations, for the induction phase and maintenance phase. To this end, Houssiau (71) described the use of cyclophosphamide (induction) and azathioprine (maintenance), or MMF (induction) and MMF (maintenance), or cyclophosphamide (induction) and MMF (maintenance), for the indicated phases. An example of commentary from this review included, "MMF was found to be superior to … cyclophosphamide at inducting complete remission." MMF is mycophenolate mofetil.

The following Clinical Study Protocol provides a detailed account of the induction and maintenance phases, as applied to SLE (72,73). The study drug was MMF. In the induction phase and in the maintenance phase each used the MMF study drug, but different comparator drugs were used for the control arm.

The Protocol outlined these two phases as, "[a]fter screening assessment and randomization, subjects will return at Week 2, Week 4, and subsequently every 4 weeks until Week 24 of the induction phase. After re-randomization into the maintenance phase, subjects will initially return 3 times in the first 3 months … [t]hereafter, subjects will return at every 3 months … until Month 36 of the maintenance phase or study termination."

According to the study design, subjects were randomized and then treated in the induction phase, followed by determining efficacy (responders), followed by randomizing the responders and then treating them in the maintenance phase. Protocol instructed that, "the total sample for the induction phase will be 358 subjects (179 per treatment group) … [a]pproximately 278 responders from the induction phase are projected to be randomized into the maintenance phase (139 in each treatment group)."

The induction phase had two arms, one arm receiving MMF and the other arm receiving intravenous cyclophosphamide (IVC). The Protocol's instructions included, "**Induction Phase.** MMF 1.5 g BID … OR IVC 0.5 to 1.0 g/$m^2$ in monthly pulses."

The maintenance phase included two arms, the MMF arm and the azithromycin arm. The Protocol's instructions included, "**Maintenance Phase.** MMF: 1 g BID with placebo matching azathioprine 2 mg/kg/day … OR Azathioprine: 2 mg/kg/day with placebo matching MMF 1 g BID … This part of the study is double-blind double-dummy. Subjects will take one active treatment (MMF or azathioprine) and the placebo matching the alternative treatment."

The fact that the active comparator drug used in the induction phase was different from the active comparator in the maintenance phase is emphasized by the Protocol's disclosure that, "[t]he active comparator during the induction phase is IV **cyclophosphamide** (0.5 g/$m^2$ to 1 g/$m^2$) … [t]he active comparator during the maintenance phase is **azathioprine** (2 mg/kg/day)."

[71]Houssiau FA. Therapy of lupus nephritis: lessons learned from clinical research and daily care of patients. Arthritis Res. Therapy 2012;14:202 (8 pp.).

[72]Clinical Study Protocol. Protocol Number WX17801. Aspreva Lupus Management Study (ALMS) (April 12, 2007).

[73]The Clinical Study Protocol was a supplement to, Dooley MA, Jayne D, Ginzler E, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. New Engl. J. Med. 2011;365:1886–95.