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8th May 2015

Re: Comments on the Assessment Report: Kidney transplantation (adults) - immunosuppressive therapy (Review of TA 85) [ID456]

Dear Meindert,

Sanofi welcomes the opportunity to provide comments on the Assessment Report produced by the Peninsula Technology Assessment Group (PenTAG) for the above appraisal.

We provide in the attached table a detailed list of comments on key aspects of the report. In summary, whilst the report's authors are to be commended for their comprehensive review of the evidence, we believe certain key assumptions are incorrect, some aspects of current clinical practice have been overlooked, and as a consequence some of the conclusions may be invalid.

Primary amongst our concerns is the synthesis of data from three different induction therapies as if they are the same product; namely Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]). The remit for this appraisal is, amongst other things, to establish clinical and cost-effectiveness of Thymoglobulin as an induction therapy, yet the data used in the evidence synthesis and economic model appears to be a combination of data for Thymoglobulin®, ATGAM® (lymphocyte immune globulin, anti-thymocyte globulin [Pfizer]) and ATG-Fresenius S® (rabbit anti-human T-lymphocyte immunoglobulin, [Neovii Biotech]), all of which are different products, produced in different ways, by different manufacturers.

We note that there is no mention of these other products or manufacturers in either the Final Scope, the Final Stakeholder Matrix, or the Assessment Group Protocol, and we can find no explanation or rationale for the combination of these data within the Assessment Group Report. We do not believe these data should be pooled as they have been, and more importantly they should not be used as the evidence-base upon which to assess Thymoglobulin's clinical and cost-effectiveness.

We believe these issues should be addressed prior to the report being provided to the Appraisal Committee.

Please let me know if you have any questions regarding our detailed comments.

Yours Sincerely,

[redacted]
Sanofi

Sanofi - May 2015

Response to the Assessment Group Report: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Section/Page	Comment
Section 4.2 Page 94: Table 9	**Four studies have been inappropriately included as Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies.** Samsel (2008), Kyllönen (2007), and Sheashaa (2008) used ATG-Fresenius and Sollinger (2001) used equine-derived antithymocyte globulin (ATGAM), not Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATGAM are anti T and B lymphocyte immunoglobulin products derived from thymus lymphocyte immunisation, but rATG is rabbit derived whereas ATGAM is horse-derived. ATG-Fresenius is an anti-T-lymphocyte immunoglobulin product derived from rabbits immunised with Jurkat cells, a lymphoblastoid cell line. Both ATGAM and ATG-Fresenius differ inherently from Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), and the three products cannot be considered interchangeable. The doses, activity and targets of the three products have been assessed seperately, and although they may be used in various induction protocols in a similar manner, there are numerous pieces of evidence to suggest that that they are not biosimilar products, and are in fact inherently different. Additionally, it has been suggested that successful induction with these products may not just be due to lymphocyte-depleting properties, but may also involve immunomodulation of other cell types, including regulatory T cells and dendritic cells (Leitner 2010; LaCorcia 2009). It is not difficult to conceive that even subtle differences in antibody content between the different products could significantly and differentially affect their activities as induction therapies. The efficacy and safety of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATGAM have been compared in a prospective randomised double-blind single-site study (Hardinger 2008), in which significant outcome differences were identified, including the composite endpoint of freedom from death, graft loss or acute rejection at 10 years (in favour of Thymoglobulin). To our knowledge, there have been no randomised controlled studies that have directly compared the efficacy and safety of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius for induction of kidney transplant patients, to discern similarity or otherwise. However, one randomised comparative study of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus ATG-Fresenius, assessing haematologic adverse effects at one month, has been reported in kidney transplant patients (Rostaing 2010). This study concluded that reduced platelet and reticulocyte counts occurred less frequently with Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), accompanied by a reduced requirement for erythropoietin-stimulating agents versus ATG-Fresenius. Another recent publication demonstrated that Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius differ significantly in terms of regulation of the intrarenal transcriptome (Urbanova 2012). Two retrospective series also have indicated significant differences in terms of white blood cell count recovery rates (Cicora 2013) and rates of delayed graft function and acute rejection (Chen 2015). Finally, in regard to the idea that Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) may benfically have immunomodulatory activity in addition to lyphocyte-depleting, Leitner 2010 determined that Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin,

	[Sanofi]) and ATG-Fresenius targets dendritic cell antigens with differential activity. All four non-Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies addressed in the assessment group's report have been incorporated into subsequent network meta-analyses for a variety of outcome measures.There is no rationale or justification provided in the assessment group's report for combining data from studies involving different lymphocyte-depleting products. The European Public Assessment report for paediatric studies of Anti-human T-lymphocyte immunoglobulin from rabbits states that although Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius have the same ATC code they actually constitute two different drug products (EMA 2014). Furthermore, please find the following quotation from an editorial piece (Mohty 2012); "Despite sharing some common properties, these different products are strictly different drugs, and have never been compared thus far in a controlled setting." A recent review (Hardinger 2012) also stated; "A recent meta-analysis of six randomized studies including 853 patients showed no differences between ATG and basiliximab for the outcomes including BPAR, delayed graft function (DGF), graft loss, and patient death [Liu 2010]. A major limitation to this meta-analysis was that authors included all preparations of ATG in the analysis". The Liu meta-analysis was not considered in the assessment group report. We believe that it is clearly incorrect to combine analyses from studies involving different products that are considered non-interchangeable. We therefore recommend that all relevant analyses should be rerun with the exclusion of Samsel (2008), Kyllönen (2007), Sheashaa (2008) and Sollinger (2001).
Section 4	**Although the scope for this MTA included immunological risk as a relevant parameter in defining subgroups, the assessment group did not present any subgroup analyses.** Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) is a potent immunosuppressing agent, used as induction therapy to suppress acute rejection of kidney transplants. However, the implications of over-suppression are potentially increased infection and malignancy rates. Therefore, it is not only important to balance safety and benefits with appropriate dosing, it is also critical to acknowledge that the risk:benefit profile may differ for patients with different levels of rejection risk. It is our understanding that in clinical practice Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) is predominantly used in patients with a moderate/high immunological risk status, where a powerful immunospuppresant may be most justified. Use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) in this setting is supported by the 2009 KDGIO guidelines and a more recent review by Hardinger (2013). Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) induction may be used in low-risk kidney transplant patients on occasion, to support calcineurin inhibitor or steroid-sparing regimens. Randomised trials of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus no induction or placebo in populations selected according to higher immunological risk have not been performed. However, one randomised trial has shown a lower rate of acute rejection for Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus basiliximab induction in patients at moderate to high immunological risk (Brennan 2006). Although studies of daclizumab (another IL-2 receptor antagonist) are not in scope for this appraisal, it should be noted that comparisons of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) with daclizumab are consistent with the Brennan findings (Noël 2009). Three other studies in lower

	risk patients found no significant benefit of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus IL-2 receptor antagonist induction (Lebranchu 2002; Mourad 2004; Abou-Ayache 2008). The benefits of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) are therefore likely to be concentrated in moderate or high-risk populations. The EMA guideline on clinical investigation of immunosupressants for organ transplantation (2009) states that best attempts should be undertaken to define immunological risk at baseline (e.g. low/medium/high). The Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies included in the assessment group's report recruited patients with different immunological risks, potentially resulting in different outcomes. Of the five Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies included in the report, two studies recruited patients with low/medium immunological risk (Lebranchu 2002; Mourad 2004) , one study selectively recruited high risk patients (Brennan 2006) and two studies were non-selective (Charpentier 2001; Charpentier 2003). In order to provide clinically relevant guidance to the NHS we believe it is important to compare the immunosuppressive efficacy of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus basiliximab according to the category of immunological risk.
Section 4.2	**The dose of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) used in some of the included studies no longer reflects clinical practice.** Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) is a potent immunosuppressing agent, used as induction therapy to suppress acute rejection of kidney transplants. However, the implications of over-suppression are potentially increased infection and malignancy rates. Therefore, it is important to balance safety and benefits by appropriate dosing. It is understood that the high cumulative dose (12.5 mg/kg) of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) used in Charpentier (2001) and Charpentier (2003) is no longer used in kidney transplantation, as the increased risk may not be offset by the benefits. Based on pharmacodynamic studies (Büchler 2013; Kho 2012), a cumulative Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) dose of 6 mg/kg is generally considered appropriate for induction therapy related to kidney transplantation. For example, the large ongoing SAILOR study is currently administering a total dose of only 5 mg/kg (Ekberg 2014). Thus, these early studies in which a dose of 12.5 mg/kg was utilised no longer reflect current practice. Given the dose-dependency of possible side effects related to Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) induction, that could potentially affect graft survival, such as post-transplant lymphoproliferative disease (Marks 2011; Hertig 2015), infection and malignancy, outcomes of Charpentier (2001) and Charpentier (2003) should not be considered relevant to current practice.
Section 4.3 Page 145: Table 30	We believe that two studies have been cited in Table 30 in error. Margreiter (2002) is a study of tacrolimus versus cyclosporine. Charpentier (2003) is a study of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus no induction. It is possible that Mourad (2004) was intended to be cited here, since the publication states that all episodes of BPAR in both treatment arms were borderline or grade I. Another reference which the authors may have intended to cite is Sollinger 2001. However, Sollinger (2001) analysed ATGAM and therefore does not apply to this analysis of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus basiliximab. Thus, the

	comment 'A statistically significant difference is seen for the most severe Banff classification 3 in favour or BAS (OR 0.04, 95%CI 0.00 to 0.65), which is reported by Sollinger (2001) should be omitted since it does not relate to Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]).
Section 4.3.1	We would like to make the assessment group aware of a new "in press" article in Transplant Immunology regarding the risk of post-transplant lymphoproliferative disease (PTLD) associated with rabbit anti-human thymocyte immunoglobulin induction (Hertig and Zuckermann 2015). This pooled analysis concludes "Overall, the risk of PTLD following rATG induction therapy with modern dosing regimens and under current management conditions appears unlikely to make an important contribution to the risk:benefit balance."
Section 7	**Inappropriate inclusion of studies.** Given our concerns (detailed above) regarding the inappropriate inclusion of some studies for Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), the effectiveness inputs and therefore the outputs of the assessment group's economic model are subject to considerable uncertainty. We recommend that the network meta-analyses used to inform the economic model and the subsequent deterministic and probabilistic results of the economic model are updated accordingly. Only five studies involve the use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), (Lebranchu 2002; Mourad 2004; Brennan 2006; Charpentier 2001; Charpentier 2003). Only three studies involve the use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) at current-practice dose levels, (Lebranchu 2002; Mourad 2004; Brennan 2006).
Section 7	**No consideration has been given to the effect of immunological risk status on the cost-effectiveness of the different treatment regimens.** As discussed above, Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) is predominately used in moderate/high immunological risk patients on the basis of evidence demonstrating that it offers benefits versus basiliximab in this patient group. In order to provide clinically relevant guidance on the use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), an assessment of cost-effectiveness should be conducted separately for patients with low and moderate/high immunological risk. Only one study involves the use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) at current-practice dose levels, and in moderate/high risk patients (Brennan 2006).
Section 7 Page 392	No rationale has been provided for the higher costs of infection prophylaxis associated with Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]). In Brennan (2006) both Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and basiliximab arms received prophylaxis.
Section 7 Page 427	It is not clear what CMV rates have been included within the model for regimens including Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) induction. In high risk patients groups, Brennan (2006) recorded a Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) mediated CMV infection rate of 7.8% versus 17.5% for basiliximab (with both treatment arms receiving prophylaxis).

Section 7 Page 472: Table 207	The presentation of cost-effectiveness results is unconventional. An incremental analysis has been provided, however the treatment regimen with the least QALYs has been used as the referent treatment as opposed to the treatment regimen that is the least costly. It should be noted that the large ICERs associated with Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) result from a very small denominator (incremental QALYs) and should be interpreted in this context. It would be helpful if the probabilistic analysis was used to provide confidence intervals for these results.
Section 7 Page 450	The assessment group's model assumes that there is no difference in monitoring costs across treatment regimens. As acknowledged in the report, clinic visits are likely to be a key driver of costs. Popat (2014) report cost savings associated with the use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) compared to IL-2 receptor antagonists. This is partly driven by a lower number of clinic visits for patients who received Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]). We acknowledge that there are important limitations of this study (as highlighted in the report); however given the relatively small and uncertain difference in cost between the induction regimens in the assessment group's cost-effectiveness analysis we believe that this study should be taken into consideration.

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