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MSD

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27th October 2010

Dear Dr Longson

RE: GOLIMUMAB FOR THE TREATMENT OF PSORIATIC ARTHRITIS – COMMENTS ON THE APPRAISAL CONSULTATION DOCUMENT (ACD)

Schering-Plough Limited, which is now part of MSD (MSD), welcomes the opportunity to comment on the ACD, which sets out the Appraisal Committee's (the Committee) recommendations on golimumab for the treatment of psoriatic arthritis (PsA).

We are disappointed that the Committee, having reviewed all of the evidence as well as hearing from stakeholders, has not felt able to recommend golimumab for the treatment of patients suffering from PsA.

MSD believes that there is a role for golimumab, based on significantly reduced injection frequency and lower injection site reactions, reducing pain and discomfort for the patient leading to a better quality of life. In addition, it provides physicians with a further treatment option to enable the more effective management of PsA. This was clearly articulated by the patient representatives and the clinical experts in both submissions to, and depositions at the Committee meeting.

In the light of the wording of the ACD as well as the discussions that took place during the open session of the Committee meeting, MSD believes that the Committee's recommendation was influenced by the unbalanced presentation of the evidence to them.

General comments follow on pages 2 – 8 and detailed comments on pages 9 – 19.

General Observations

MSD considers that the ACD is misguided in the following respects:

- The Committee's apparent use of a single efficacy criterion to decide on the relative clinical efficacy of golimumab compared with infliximab, adalumimab and etanercept; compounded by inappropriate use and interpretation of the outputs from various mixed treatment comparisons.
- The undue weight given by the Committee to using safety as a decision criterion.

MSD takes the view that the relative weighting attached to each of these by the Committee, further details of which are set out below, in arriving at the provisional recommendation under discussion lays the recommendation open to challenge from a process perspective.

A. Reliance on one treatment efficacy measurement as assessed within the Mixed Treatment Comparisons methodology to inform decision making around comparative efficacy

1. Single treatment efficacy criterion

Patients with a diagnosis of PsA are a heterogeneous group and in response to this a number of instruments have been developed to evaluate the efficacy of management strategies, including pharmacological treatments. For example, the GO-REVEAL study (Kavanaugh, et al, 2009) measured the following:

- Psoriatic Arthritis Response Criteria (PsARC)
- Psoriasis Area and Severity Index (PASI)
- American College of Rheumatology 20% improvement criteria (ACR20)
- American College of Rheumatology 50% improvement criteria (ACR50)
- American College of Rheumatology 70% improvement criteria (ACR70)
- Health Assessment Questionnaire (HAQ)
- Nail Psoriasis Severity Index (NAPSI)
- EULAR response
- Disease Activity Score (DAS28-CRP)
- Enthesitis assessment
- Morning stiffness assessment
- Dactylitis assessment

It appears that the Committee has focussed primarily on only one efficacy measure, the HAQ, which is a self-reporting assessment of functional ability, when deciding on the clinical efficacy of golimumab.

This approach is not consistent with current clinical practice or previous NICE guidance in this area, where the measurement of effectiveness is assessed by reference to joint response; PsARC, or the American College of Rheumatology improvement criteria (ACR), plus the use of PASI to assess skin response.

In addition, the recently published guidance TA199 -Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, support this approach:

> *"The Committee considered the clinical-effectiveness data presented by the manufacturers and noted that etanercept, infliximab and adalimumab all showed a statistically significant response in the joint disease (PsARC, ACR) and skin disease (PASI) criteria at 12-week and 24-week follow-up compared with placebo"*
> *"..... Although the indirect comparison conducted by the Assessment Group suggested that infliximab is the most effective treatment overall, taking into account both skin and joint disease, the Committee concluded that there was not enough evidence to indicate clinically important differences in the effectiveness of individual TNF inhibitors in the treatment of psoriatic arthritis. (4.3.3."*.

The British Society of Rheumatology (BSR) Guidelines for the use of TNF Inhibitors in patients with PsA recommends an assessment of PsARC and PASI together to assess response to treatment[1].

Where alternatives are chosen, the decision is still based on use of an instrument that examines response across a range of measures. For example, this approach was followed in a recent analysis from the BSR by using the European League Against Rheumatism (EULAR)[2].

2. Mixed Treatment Comparisons

The use of the HAQ score in (virtual) isolation is compounded by the effect of the methodology used to compare golimumab with etanercept, adalumimab and infliximab, namely, Mixed Treatment Comparisons (MTC).

MTCs potentially have a role in guiding an understanding of whether a range of technologies may be comparable in the absence of head to head data. Caution should however be exercised when using the findings from such a methodological approach to support ranking decisions within a class/group of technologies.

The 2008 Methods Guide to Process[3], references the use of indirect comparisons and mixed treatment comparisons but fails to clarify the uncertainty associated with the use of such methodologies. As such caution should be used when considering how to reflect any findings in Committee decisions.

In the last three years, the NICE Executive has apparently moved from a position of accepting that MTC methodologies *may* provide supporting evidence to inform the decision of a Committee faced with uncertainty, to one of accepting that a

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[1] (Kyle et al, 2005).

[2] (Saad et al, 2010).

[3] (http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Committee can use the results from such an analysis to *reliably* make ranking decisions within a class of technologies.

Whilst MSD supports the development of alternative methodologies to inform decision making by payers it does not believe that MTCs can ever be used as a credible alternative to 'head to head' &/or placebo controlled RCTs, to safely support clinical decision making that involves choice within a class of drugs.

Methodological experts, experienced in clinical data analysis, have expressed concerns regarding the robustness of the MTC methodology over and above the information provided from primary RCTs[4].

The Cochrane collaboration[5] arguably comprises the grouping of people most interested in, and knowledgeable about, synthesis of clinical data to aid clinical decision making. MTCs are an ongoing point of interest with a number of experts experienced with MTC methodology and they have consistently indentified that caution needs to be used when attempting to apply findings to clinical decision-making compared with use of results from original RCTs.

A recent analysis to establish whether MTCs can ever provide a robust platform for clinical or payer decision making has provided evidence that all such analyses are likely to be underpowered in relation to being able to support ranking decisions about a group of technologies.[6]

B. 'Safety' as a decision criterion

The safety of the medicines we develop is a priority for the company. As well as adhering to all of the regulatory requirements regarding safety in the field of TNF Inhibitors and specifically related to golimumab, we have committed ourselves to undertake or support:

- A registry of patients prescribed golimumab in Germany
- A registry of patients prescribed golimumab in Sweden
- A five year follow-up study of all patients treated with golimumab in the GO-REVEAL (Psoriatic Arthritis), GO-FORWARD (Rheumatoid Arthritis patients with inadequate response to methotrexate), GO-RAISE (Ankylosing Spondylitis), GO-BEFORE (Rheumatoid arthritis patients who are methotrexate naïve) and GO-AFTER (Rheumatoid arthritis patients previously treated with other TNF Inhibitors) studies.

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[4] (Gubing et al, 2006; Bucher et al, 1997; McAlister et al, 1999; Lumley et al, 2002).

[5] Ades T, Caldwell D, Song F, Altman D, Higgins J, Bucher H, Guyatt G, Mills E;

http://www.cochrane.org/multimedia/multimedia-cochrane-colloquia-and-meetings

[6] (Mills et al, 2010 - Academic in Confidence - paper provided on request).

- Commitment to provide a physician education programme in all countries where golimumab is/will be marketed.

MSD recognises that the Committee has a legitimate interest in understanding the safety of a technology under their purview from the position of any differences in adverse event rates as they would affect a cost utility analysis. Where we do have a concern is around the Committee's focus on the safety of golimumab *per se*.

The ACD clearly reflects the Committee's concerns regarding safety. The ACD is also a fair reflection of the Committee meeting itself, where a significant part of the open session revolved around a discussion about the safety of golimumab driven by a focus on adverse event reports from the GO-REVEAL study. We would however like to note that the Committee was reminded on three occasions that the GO-REVEAL study was not sufficiently powered to examine safety.

During the open session of the meeting, no mention was made of the fact that the EMEA had reviewed the same data when deciding on whether to grant the product its licence and had concluded that the safety profile was favourable enough to warrant licensing.

In addition to considering safety data when granting a licence, the EMEA also has an ongoing role in monitoring the safety of a drug post the granting of a licence. Clearly, this cannot also be the role of NICE.

In the light of the above, we feel that the Committee should take the following into account in its further deliberations:

1. NICE remit

MSD is concerned that NICE, through the actions of the Committee, is acting at odds with the NICE Guide to the Single Technology Appraisal (STA) process.[7] This includes the following definition of the Medicines and Healthcare Products Regulatory Agency (MHRA)

> *"The Executive Agency of the Department of Health. It protects and promotes public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely".*

That NICE acknowledges the role of the MHRA in ensuring the safety of medicines in the UK reflects our understanding of the difference between the two agencies. We note that the role of NICE as set out in the Directions from the Secretary of State[8] does not define, for medicines, any role regarding evaluating safety and by extension does not require NICE to consider long term safety data

[7] http://www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf

[8] http://www.nice.org.uk/niceMedia/pdf/DirectionFromSecretaryOfState2005.pdf

(other than in relation to comparators around relative adverse event rates) in the Committee's decision-making process.

2. Guidance issued by NICE regarding TNF Inhibitors as a class

MSD recognises that each of the four NICE guidance Committees is independent and also could, in principle, produce a different set of recommendations from other Committees, having deliberated upon the same evidence base.

Despite this, MSD understands that the NICE Executive has a role in providing advice to its Committees based on previously generated and related NICE guidance so as to achieve coherence and consistency. This is done, if not for the sake of the patients and clinicians affected by NICE guidance, to allay potential concerns regarding the robustness of the process underpinning NICE guidance and to reduce the potential grounds for appeal.

Regarding consistency of recommendations, previous Committees have reflected on the long term safety of TNF inhibitors. They have concluded that for a new technology which does not possess long term efficacy and safety data, the consideration of the importance of this should be left jointly to the patient and clinician as one of a number of factors that are considered in reaching treatment decisions. An exhaustive review of comments from NICE guidance regarding the safety of TNF Inhibitors provides the following support:

a) TA180. Ustekinumab for the treatment of adults with moderate to severe psoriasis.
"The Committee heard from the clinical specialists that ustekinumab is a new drug that has been given to far fewer people than the other biological therapies, and therefore its long-term safety profile is less certain. Because of this, the specialists considered that the drug may initially be prescribed more cautiously than existing treatments. The Committee also heard from the clinical specialists and patient experts that people with severe psoriasis are often well informed about drug safety and able to consider benefits and risks before starting treatment (section 4.4. p.16)".
No mention is made in this guidance of the stated uncertainty driving any concerns re: comparative cost-effectiveness.

b) TA186. Certolizumab pegol for the treatment of rheumatoid arthritis.
No mention of safety either in principle or in relation to any long-term uncertainty regarding cost-effectiveness.

c) TA187. Infliximab (review) and adalimumab for the treatment of Crohn's disease.
The following mention is made of safety re: infliximab and adalimumab:
"The Committee heard from the clinical specialists that they were concerned about the longer-term effectiveness and safety of infliximab and adalimumab".

This did not translate into a decision by the Committee to restrict access, or to any (expressed) long-term uncertainty regarding comparative cost-effectiveness.

It should be noted that this concern about longer-term (effectiveness and) safety relates to two technologies which had been in use in the UK for a number of years; the conclusion being that expert clinicians would only be confident about the longer term safety of *any* of the TNF inhibitors, after a significant number of patients had received one or other of the TNF inhibitors over a number of years far in excess of any of the available currently licensed TNF inhibitors.

d) TA198. Tocilizumab for the treatment of rheumatoid arthritis
A discussion describes comparable AE rates with other TNF Inhibitors and the following statement appears:
"Approximately 14% of people discontinued tocilizumab treatment for safety reasons (including intercurrent illness)".

e) TA199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.
Given that this Technology Appraisal (TA) is a recently updated Multi Technology Appraisal (MTA) (published August 2010) providing guidance for the three comparative therapies included in the golimumab appraisal (infliximab, adalumimab, etanercept) and for the same disease, it is arguably not only the most relevant, but also likely to be the most helpful in guiding related decision-making.

In TA199, when referring to adverse events rates for each technology, the following comment is made for each one when it is described in the guidance:
"For full details of undesirable effects and contraindications, see the summary of product characteristics."

The guidance goes on to state:
"Overall, the limited evidence prevented them from drawing firm conclusions from the systematic review about the comparative adverse event profile of the three TNF inhibitors".

The statements above are supported by two systematic reviews[9] and a recent review of data regarding patients with a diagnosis of PsA within the British Society of Rheumatology Biologics Registry (BSRBR).[10]

3. STA process

The scope for the appraisal of golimumab in patients with psoriatic arthritis is stated as follows:

[9] Saad et al, 2008; Ravindran et al, 2008

[10] Saad et al, 2010

"To appraise the clinical and cost-effectiveness of golimumab, within its licensed indication, for the treatment of psoriatic arthritis."

Safety is not included in the remit, although within the scoping document one of the outcomes stated to be measured is 'adverse events'.

As a stakeholder, MSD understands that the measurement of adverse events is a necessary component for a comprehensive cost utility analysis, where the cost of treating such events could influence the final Incremental Cost Effectiveness Ratio (ICER).

MSD also understands that this is divorced from the Committee making decisions about whether a product should be approved or not based on the presence/absence of long-term safety data.

Detailed comments

Clinical efficacy of golimumab in relation to etanercept, infliximab and adalumimab

MSD believes that a key determinant of the recommendation within the ACD is driven by the belief that etanercept is clinically superior to golimumab. The weight that must have attached to this within the decision-making of the Committee is provided by a comment from the Evidence Review Group (ERG) report:

> *"However, a key area in determining the cost-effectiveness of anti-TNF agents is whether they should be considered equally clinically effective, that is, to treat them as a class. This was the position adopted in the guidance issued by NICE following the previous appraisal of etanercept, adalimumab and infliximab for psoriatic arthritis. If all anti-TNF agents are considered equally effective (in terms of PsARC, HAQ[11] and PASI responses) then etanercept, adalimumab and golimumab have very nearly equal costs and equal QALYs and all have an ICER of about £15,000 per QALY versus palliative care [ERG report – section 1.5]".*

The issues around this apparently breakdown into:

1. Focus on a single measure of effectiveness; the HAQ score.
2. Reliance on MTC results to inform the Committee decision.

1. Focus on a single measure of effectiveness

In the above quote from the ERG report, we note that they have included HAQ as one of the three response criteria. This stands apart from; TA199 guidance which discusses response in relation to PsARC, ACR and PASI, whilst BSR guidelines mention two (PsARC and PASI). Neither TA199 nor the BSR Guidance suggest that HAQ is a key criterion for assessing clinical efficacy of TNF Inhibitors.

This ERG highlighting of HAQ as one of the response criteria, is reflected throughout their report. It was also highlighted in the clinical presentation to the Committee, and is reflected in the ACD itself. This is also consistent with the York approach to TA199 although notably this was not reflected in the TA199 Committee deliberations or decision-making.

The Committee has primarily focussed on just one efficacy measure, HAQ, when deciding on the relative clinical efficacy of golimumab. This does not conform either to current clinical practice or previous NICE guidance in this area, and may have been driven by the approach of the ERG to evidence analysis and its subsequent presentation.

2. Reliance on MTC results to inform the Committee decision

The NICE methods guide makes the following statement;

[11] HAQ was not one of the key determinants of relative efficacy used in TA.199; the three cited are PsARC, ACR and PASI.

When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework ***if it is considered to add information that is not available from the head-to-head comparison (emphasis added).***

MSD believes that the MTC does not add to the understanding of golimumab in relation to infliximab, adalumimab and etanercept.

The principal rationale for the MTC approach within Health Technology Appraisal, over and above an adjusted indirect comparison approach, lies where there is a mix of data ('head to head' studies and placebo controlled studies). In the analysis under consideration all data is from placebo controlled studies each of a single TNF Inhibitor.

The Committee's view that etanercept is clinically superior to golimumab is based on an analysis of three MTCs, namely, MSD's MTC for their submission (MS MTC), MSD's adapted MTC with inputs requested by the ERG (MS/ERG MTC)[12], and an MTC developed by the ERG (York MTC).

The ERG, and subsequently the Committee, concentrated on the comparative analysis of HAQ scores within the MTCs. MSD does not agree with this approach. MSD believes that HAQ scores have been promoted and used because they drive the potential for differentiating the technologies on cost-effectiveness grounds and therefore support an incremental ranking of the four TNF inhibitors in terms of dominance and extended dominance.

MSD's key concern around the applicability of these MTC analyses lies in the heterogeneity between the original RCTs included in the analysis with all three MTCs (reliant on the same 7 RCTs) generating different findings for a number of outcomes, especially HAQ scores.

In relation to HAQ, a comment within the ERG report states:

"Despite some differences in the mean HAQ score at baseline between the included trials, there was a high variability of these HAQ values (high standard deviation) and, thus, it is very likely that differences in mean HAQ scores were not significant. Although there was a concern about the correlation between baseline HAQ scores and absolute HAQ changes in these PsA patients, given such a high variability of these HAQ values, ***the ERG considered the exchangeability of mean HAQ scores across the included trials in the MTC analysis to be acceptable." (emphasis added)***

MSD does not believe that ERG's approach above should be adopted. The ERG's approach has a significant impact on the comparative analysis given the width of

[12] MS/ERG MTC was adapted at the request of the ERG not because of errors but rather to conform to the York understanding of TA199

the CrIs and the overlap with placebo, with a particular concern about the role of one of the etanercept studies . [13]

As a result of the more standardised and/or broader nature of the instruments, the PsARC and PASI results are more in line with the underpinning RCTs and the clinical understanding of the relative efficacy of the four technologies.

In relation to the use of MTCs for golimumab, the GO-REVEAL study provided HAQ data for the analysis. Absolute changes in HAQ score were subsequently available to both MSD and the ERG.

In contrast to this, MSD was forced to use the York analysis[14] as the data source for the etanercept trials given the absence of (appropriately presented) HAQ data from the published study reports. The York analysis builds on Commercial In Confidence (CIC) data on HAQ change with etanercept that are not publicly available (or, in the case of Mease 2000, not available for the groups of responders and non-responders separately).

MSD believes that the Mease 2000 data should have been removed from the MTC because:

1. It reported an average change in HAQ using aggregated HAQ changes of -0.1 with placebo or -1.2 with etanercept, i.e. a difference to placebo of -1.1. In the results of the MS/ERG MTC, the average HAQ change associated with etanercept (averaged across the response groups) is estimated as -0.57, the difference to placebo is -0.52. This is a composite estimate of Mease 2000 and Mease 2004 and within the framework of the MTC.

   MSD cannot be precise about the values that went into the York meta-analysis without access to the CIC etanercept data, but if the mean difference in the York analysis is -0.52 and in Mease 2000 is -1.2, then in Mease 2004 it must be smaller in magnitude than the composite mean (possibly -0.4 or -0.3 or so, depending on the size of the studies and variation between patients). *The corresponding value for those patients in receipt of golimumab 50mg from the GO-REVEAL study was -0.33.

2. 34% of etanercept-treated patients achieved a HAQ score of '0'. This dramatic improvement has not been replicated in either Mease 2004 or the etanercept RA studies.

We understand that the smaller study Mease 2000 (sixty patients, single centre and also reported in 2000) is adding significantly to the improvement in HAQ changes seen with etanercept. It would be appropriate, given the discrepancies noted above, to conduct an analysis excluding Mease 2000. MSD believes that this analysis would be more relevant for understanding the comparative HAQ values

[13] (Mease et al, 2000).

[14] Woolacott et al, 2006

given, not only the markedly differing HAQ values above, but also the other differences illustrated in Table 1.

Table.1: Selected Mease2000, Mease2004 and GO-REVEAL study characteristics.

	GO-REVEAL 2009		Mease 2000		Mease 2004	
	Golimumab 50 mg	Placebo	Etanercept	Placebo	Etanercept	Placebo
No. of patients	146	113	30	30	101	101
Centres	58		1		17	
Centre locations	USA, UK, Canada, Spain, Poland Belgium		USA		USA	

For HAQ, the lower bounds of the 95% CrIs for golimumab and infliximab overlap the upper bound of the 95% CrI for placebo. This raises further questions regarding the applicability of the findings from the MTCs as trial results were each statistically significant and infliximab was suggested as being the more efficacious of infliximab, etanercept and adalumimab in TA199.

With the combination of significant uncertainty re: the validity of some of the HAQ data plus the evidence for significant heterogeneity between Mease2004 and Mease2000, MSD does not believe that the HAQ data as currently described can be used to help inform any comparative analysis, whether in isolation or as part of a composite.

An examination of the differences between three data analyses, HAQ from the MS/ERG MTC (Figure 1) PsARC from the MS/ERG MTC (Figure 2) and PASI from MS/ERG MTC (Figure 3) demonstrates the challenges of arriving at meaningful conclusions because of inconsistent of results across instruments and issues concerning heterogeneity from the core data.

Figure 1: HAQ responders – MS/ERG MTC

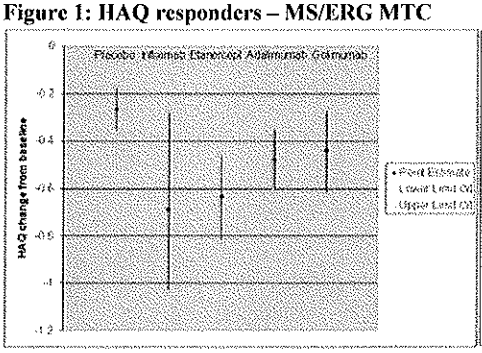


Figure 2: PsARC responders – MS/ERG MTC

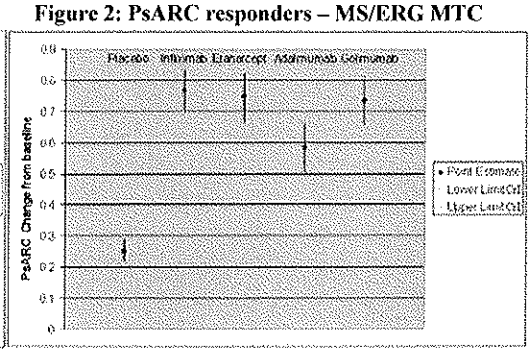
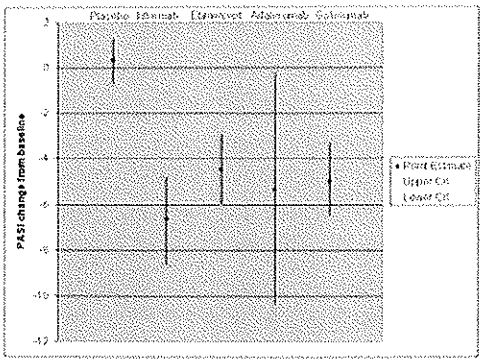


Figure 3: PASI responders MS/ERG MTC



The PASI responders (Figure.3) and PsARC responders (Figure.2) analyses point estimates and CrIs conform to the clinician understanding of drugs in this class and validate the conclusions reached in TA.199 regarding comparative clinical efficacy.

This data demonstrates the importance of evaluating effectiveness of a drug by multiple parameters instead of only one.

3. Role of HAQ scores within economic evaluation

The uncertainty regarding the 'true' HAQ value for etanercept will logically follow through to any cost-effectiveness analysis using it.

Given the uncertainty, MSD would argue that even if a ranking approach to incremental cost-effectiveness aided decision-making, it would need to exclude etanercept. The alternative would be to apply the lower of the three HAQ values from infliximab, golimumab and adalumimab to etanercept.

Absence of long-term safety data

The Committee has placed significant emphasis on safety in arriving at its preliminary recommendation

The Committee devoted the majority of the open session of their meeting to discussing the safety of golimumab and particularly events that occurred in the GO-REVEAL trial, even although it was accepted that this trial, GO-REVEAL, was not powered to examine safety.

There was also discussion around the significance of the half life of golimumab in relation to concerns about, and management of, intercurrent infections.

Golimumab half life

"The half life of Simponi (golimumab) is 12 +/- 3 days" which is similar to that of adalimumab (SPC states approximately two weeks), infliximab (SPC states 7.7-9.5 days) and etanercept (SPC states approximately 4.3 days Of note, in the Phase 3 PsA study with SC golimumab through Week 104, the incidence of serious infections per 100 subject-years follow up was 9.41 (CI: 2.56, 24.08) in the placebo group (subjects treated with placebo at Week 0 through a change in treatment to golimumab or the last safety visit), 0.84 (CI: 0.17, 2.45) in the golimumab 50 mg group, and 1.20 (CI: 0.33, 3.07) in the golimumab 100 mg group with the 95% CI's for the golimumab groups excluded from or overlapping the placebo group. These rates are similar to those reported in the Humira (2.4 per 100 subject-years[15]"

Regarding intercurrent infections, physicians who prescribe TNF Inhibitors are both familiar with the risks and are also best placed to manage intercurrent infections.

[redacted]

[15] (Mease et al,2009).

[redacted]

[redacted]

Dose escalation of golimumab affecting its cost-effectiveness

It appears that the Committee has decided that dose escalation will occur to a degree significant enough to make golimumab not cost-effective for use in England and Wales, although the clinical opinion provided to the ERG and the Committee differs.

It remains our position that dose escalation from 50mg to 100mg will not occur except in rare instances.

1. Dose escalation per label is only allowed for subjects greater than 100kg and is unlikely given UK clinical practice.

This is based upon the SmPC. The part of the SmPC in section 4.2 that discusses dose escalation does not refer to dose escalation in the general PsA patient population; rather it states that for patients weighing greater than 100 kg who have not achieved a clinical response after 3 or 4 doses, increasing the dose of golimumab to 100mg once a month may be considered. Additionally, continued therapy is recommended to be reconsidered for those patients who do not show improvement after 3-4 doses of 100mg.

> *"In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in* patients *who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg."*

MSD is aligned with clinical experts familiar with UK clinical practice in believing that dose escalation for patients who weigh less than 100kg will not occur and is not per SmPC guidance.

For the small group of patients who weigh more than 100kg (7% of the BSR registry) the SmPC does not *recommend* dose escalation in those patients who have an inadequate response; rather it states that it *may* be considered:

> *In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.....'*

The EMEA rationale for including this in the SmPC is that patients who weighed >100kg treated with golimumab 100mg from the outset fared better than those treated with 50mg from the outset. For the group of patients weighing >100kg treated initially with golimumab 50mg who were dose escalated to 100mg there was no evidence of increased efficacy.

Our position is supported by the clinical experts at the Committee meeting (aligned with the feedback to the ERG from the clinician they consulted) who stated that irrespective of weight they were far more likely to switch their patient who wasn't responding to the initial TNF Inhibitor, to an alternative TNF Inhibiter or other biologic rather than dose escalate.

2. Dose escalation in the study is not indicative of what occurs in clinical practice.

Given that the Committee, after reflecting on all of the above, believes that dose escalation is a significant issue, MSD wishes to reiterate that the proportion of patients who were likely to be dose escalated to 100mg within the GO-REVEAL study is not an indication of the degree of dose escalation likely to occur in clinical practice. The reason for this is that the GO-REVEAL trial design resulted in the dose escalation rather than individual clinical decision-making.

Within the GO-REVEAL study there was a mandatory 'early escape' where dose escalation[16] occurred in a blinded fashion if patients had a <10% improvement from baseline for both swollen and tender joints (blinding maintained). In the golimumab 50mg arm 20% of patients still receiving study medication at this stage were dose escalated. This would not be repeated in clinical practice in England and Wales. There are several reasons for this:

1. A number of the patients dose escalated would be considered non-responders in clinical practice and therefore be discontinued treatment.
2. Stopping rules as currently used in the UK would mean that the patients who were 'partial responders at the 'early escape' time point in the clinical study would be continued on treatment for 6 months. There is good evidence from the other TNF Inhibitors that for some patients it can take this long see the full benefits of the treatment.

[16] either placebo to golimumab 50mg, or golimumab 50mg to golimumab 100mg or golimumab 100mg to golimumab 100mg

3. There are alternative treatment options for patients who fail, or do not respond adequately, to an initial treatment option and clinicians have expressed a preference for switching the treatment given the evidence that patients who do not respond (adequately) to one biologic technology often do to another. There was no option within the trial design to discontinue study medication with a view to treating the patient with an alternative TNF Inhibitor or other biologic.

[redacted]

[redacted]

It is possible that the Committee conclude in its final guidance that there is no compelling evidence to support dose escalation to a total of 100mg pcm and therefore does not recommend clinicians to do so from the perspective of cost-effectiveness. Given that there is no direct clinical data supporting dose escalation for patients weighing >100kg, MSD will not be advocating dose escalation and would thus not be marketing golimumab at odds with such a recommendation were it to be included in the final guidance.

Conclusion

MSD believes that the Committee arrived at their preliminary recommendation based on a misinterpretation of the evidence.

MSD is confident that if the Committee reviewed the evidence in light of the points made in this letter it would arrive at a different conclusion; one which would enhance the physicians armamentarium and also provide a valuable option for patients who need flexibility in their treatment regimen to maintain a reasonable quality of life.

For this reason we would urge the Committee to reconsider its decision based on the evidence presented above. MSD will cooperate in the provision of any other information or analyses that the Committee might wish to review so as to enable such a re-evaluation.

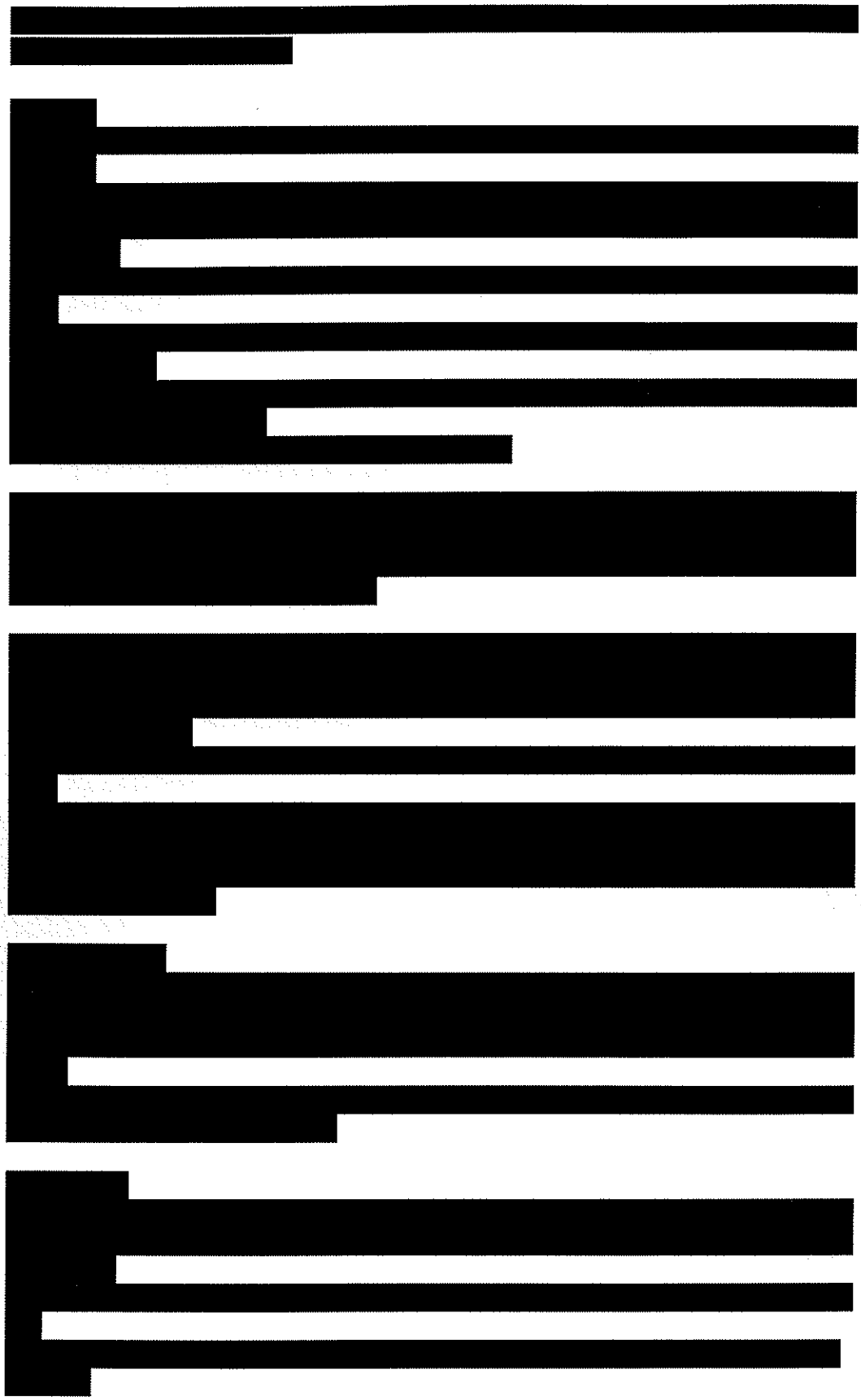
We are grateful for the opportunity to comment on the ACD and look forward to continued dialogue with NICE regarding the issues raised in this response.

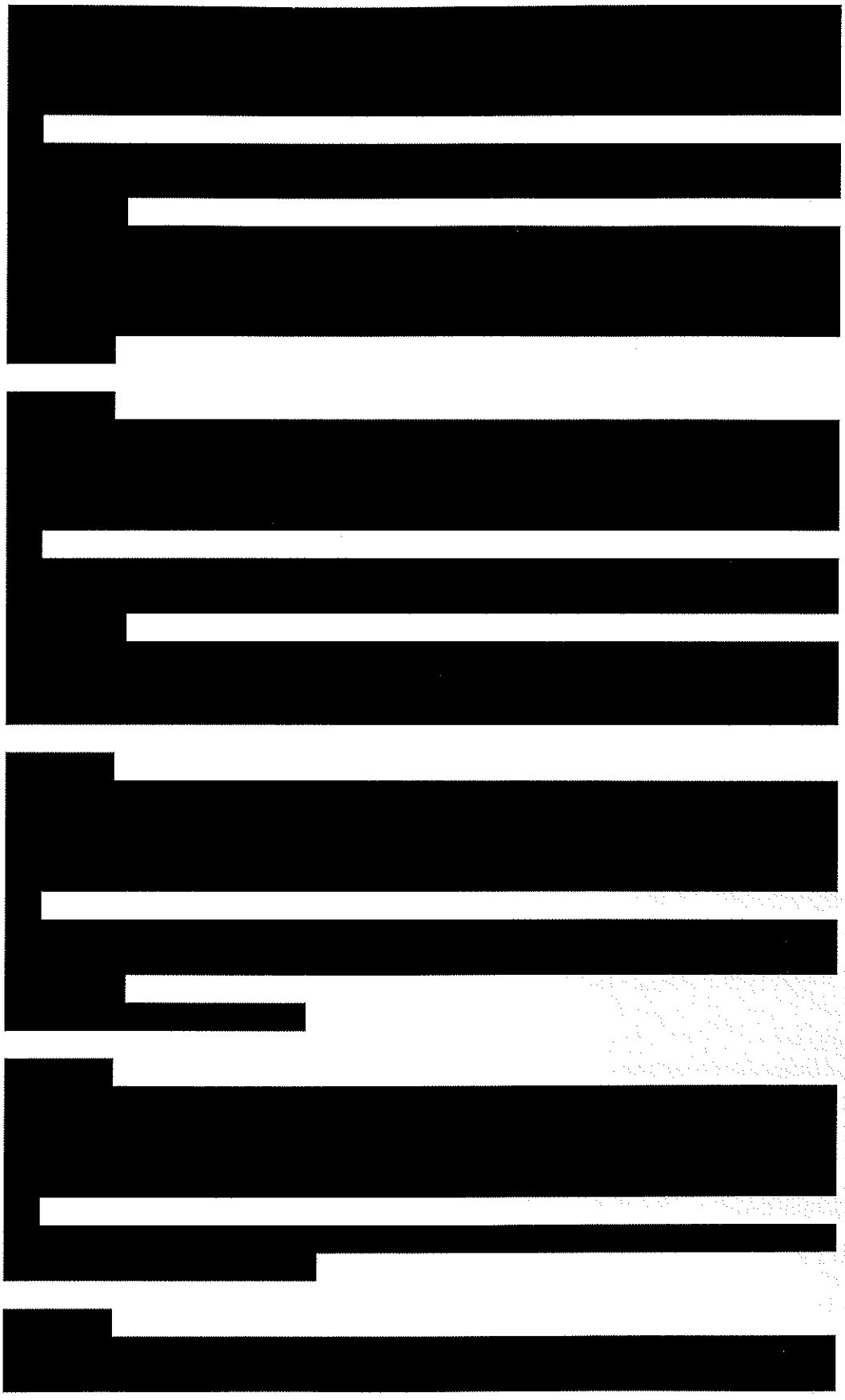
Sincerely

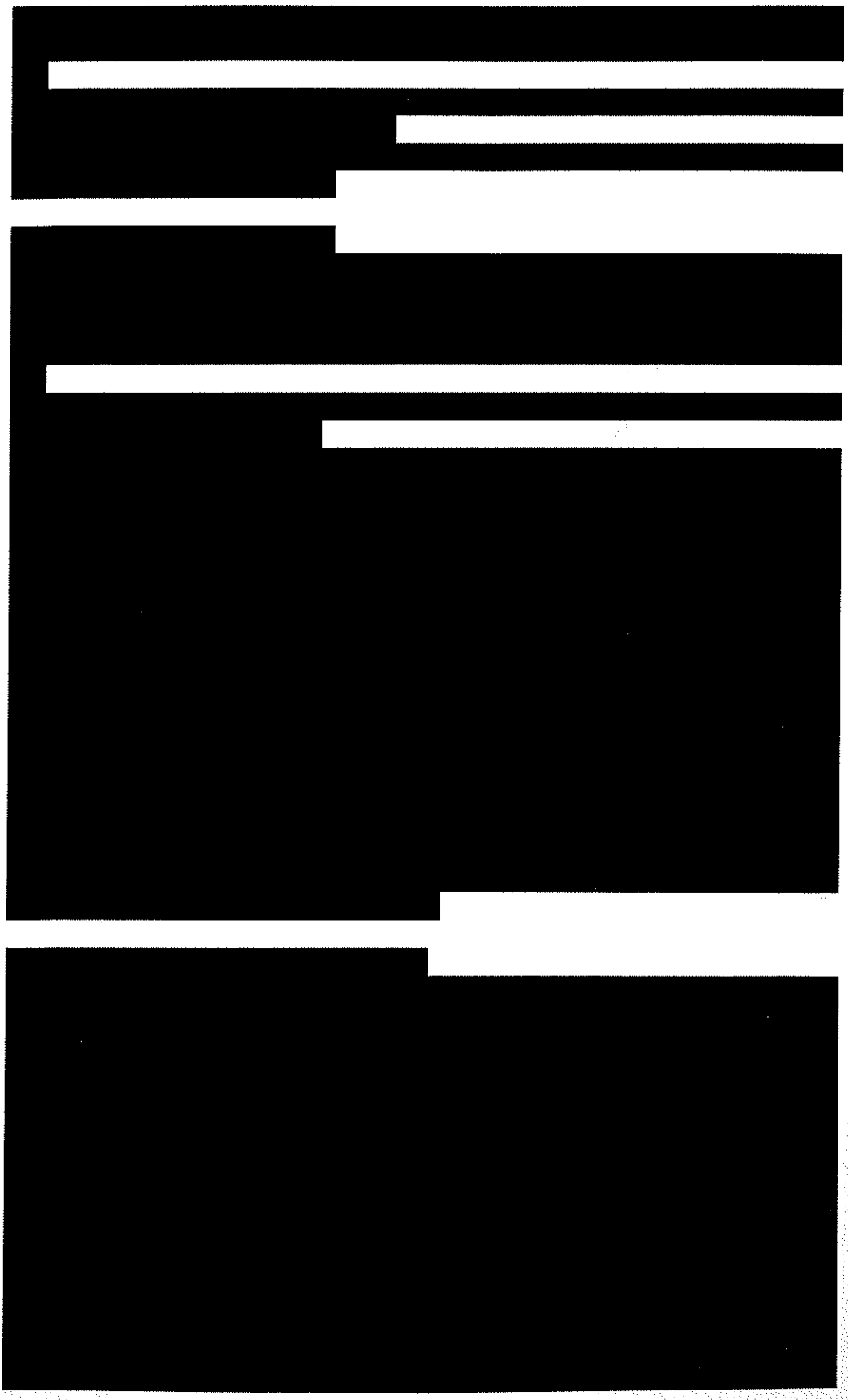
[redacted]

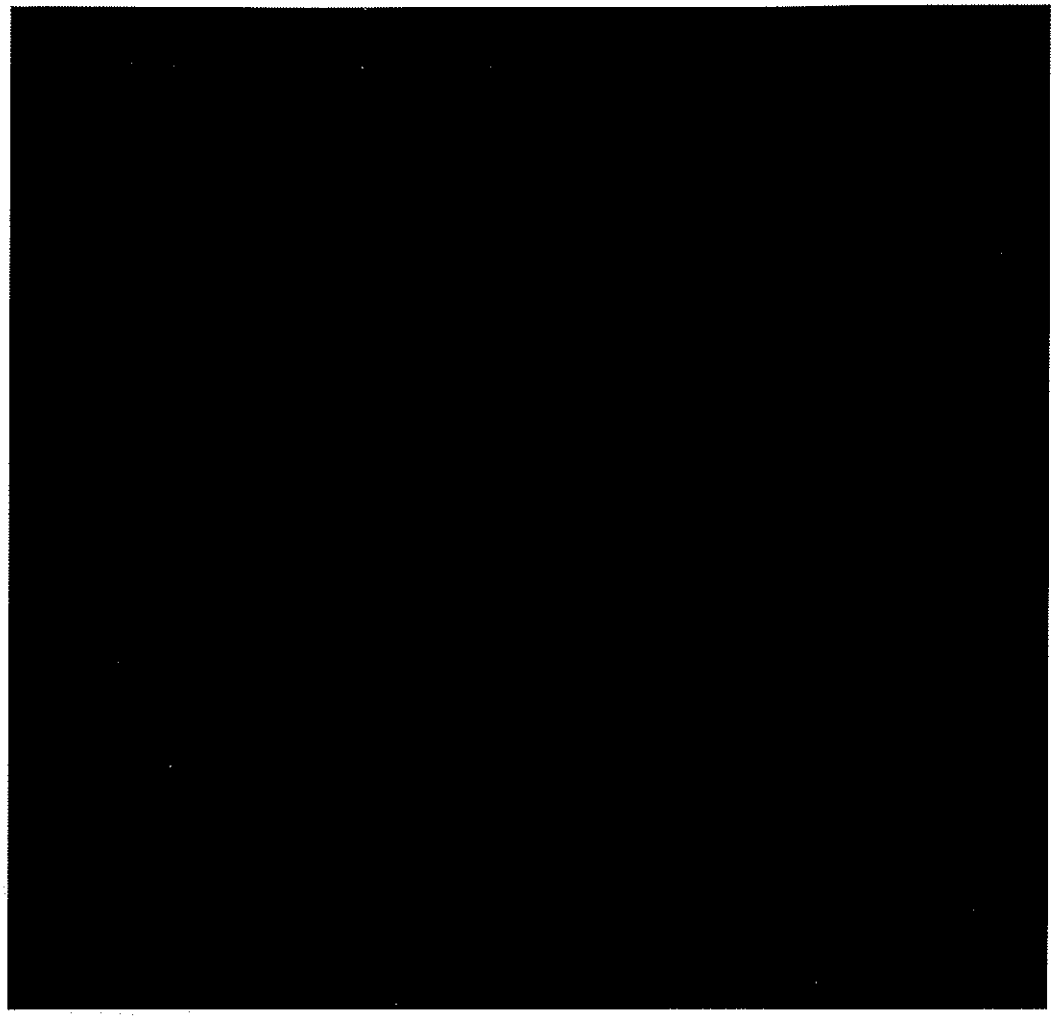
[redacted]

MSD

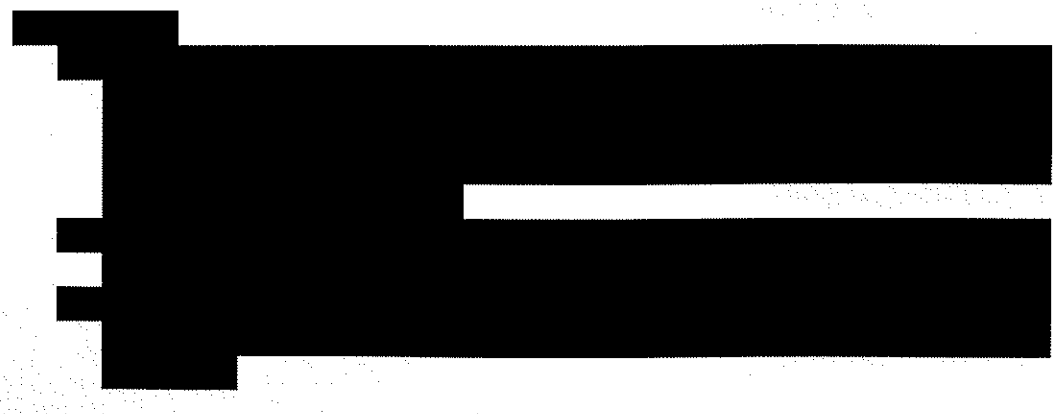










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