17 January 2013
EMA/735864/2012
Committee for Medicinal Products for Human Use (CHMP)

# Cellcept

(mycophenolate mofetil)

Procedure No. EMEA/H/C/000082/A46/034

# CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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# Administrative information

| | |
|---|---|
| Invented name of the medicinal product: | Cellcept |
| INN (or common name) of the active substance(s): | Mycophenolate mofetil |
| MAH: | F. Hoffmann- La Roche Ltd |
| Currently approved Indication(s) | CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. |
| Pharmaco-therapeutic group (ATC Code): | Immunosuppressive agents ATC code L04AA06 |
| Pharmaceutical form(s) and strength(s): | Capsules, hard 250 mg<br>Tablet 500 mg<br>Powder for concentrate for solution for infusion 500 mg<br>Powder for oral suspension 1 g/5 ml |

# Introduction

On 9th November 2011, the MAH submitted a clinical expert overview for Study WX17801, in lupus nephritis, with CellCept (mycophenolate mofetil), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of the follow up measure 034.

The MAH stated that the submitted paediatric data do not influence the benefit risk for CellCept and that no consequential regulatory action is required.

Background

A final clinical study report for protocol WX17801 was submitted as part of FUM 026 on 20/12/2010: 'A prospective, randomized, active controlled, parallel group, multi-center trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission in subjects with lupus nephritis. '

This study was discussed by CHMP because of higher death rates in patients receiving MMF, compared to intravenous cyclophosphamide (IVC) during the induction phase. On 21/03/2011, CHMP concluded that the imbalance in deaths was most likely a chance finding, in view of the subsequent assessment of the maintenance phase, in which safety was comparable to the comparator azathioprine (AZA).

CellCept contains mycophenolate mofetil (MMF), which is a pro-drug. Orally-administered MMF undergoes complete pre-systemic metabolism and is converted into the active metabolite mycophenolic acid (MPA). MPA acts by inhibition of inosine monophosphate dehydrogenase (IMPDH), which is required for guanosine nucleotide biosynthesis. MPA has marked cytostatic effects on T- and B-lymphocytes because they depend on *de novo* synthesis of nucleotides for their proliferation. Other cell types can use alternative pathways for purine synthesis – the cytostatic effects of MPA on such cells do not appear to be marked.

Mycophenolate mofetil is well-established in the treatment of post-transplant patients. In recent years clinical trials have been conducted in the treatment of autoimmune diseases, including lupus nephritis.

The current approved indication is:

*CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.*

Cellcept is approved in children (aged 2 to 18 years) post-renal transplantation. The SmPC states that there is no data available for paediatric hepatic or cardiac transplant patients.

# Scientific discussion

## *Information on the development program*

The MAH stated that Study WX17801 *A prospective, randomized, active controlled, parallel group, multi-center trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission in subjects with lupus nephritis* is a stand alone study.

## *Information on the pharmaceutical formulation used in the study*

The paediatric subjects were aged 12-18. CellCept was administered as 500mg tablets.

## *Clinical aspects*

### *1. Introduction*

The MAH submitted an expert clinical report and final protocol for:

Study WX17801: A prospective, randomized, active controlled, parallel group, multi-center trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission in subjects with lupus nephritis.

### *2. Clinical study (WX17801)*

**Description**

This Phase III study was a prospective, randomized, active controlled, parallel group, multi-centre trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission in subjects with lupus nephritis (LN).

The study was conducted at 71 centres in 19 countries, and completed in 2010. The sponsor has stated that the study was conducted in compliance with GCP.

The study consisted of 2 phases: an induction phase and a maintenance phase. During the induction phase, subjects were randomized in a 1:1 ratio to receive open-label MMF or intravenous cyclophosphamide (IVC) for 24 weeks. At the end of the induction phase, subjects who showed a response (decrease in proteinuria and stabilization or improvement of serum creatinine) or complete renal remission were eligible for randomization into the maintenance phase. In the maintenance phase, subjects were randomized in a 1:1 ratio to receive double-blind MMF or azathioprine (AZA) until the last subject to enter the maintenance phase had been followed for 36 months.

**Induction phase**

**Methods**

- Objective(s)

The primary efficacy objective for the induction phase was to demonstrate superiority of MMF therapy compared to IVC in inducing response in patients with lupus nephritis at 24 weeks.

- Study design

This was a randomised open-label, parallel group study comparing MMF and IVC. Subjects were assigned 1:1, stratified by race/ethnicity and biopsy class.

Subjects were withdrawn at week 12 if their serum creatinine was 30% or more above baseline (based on 2 consecutive measurements separated by at least 4 weeks) or if they required other immunosuppressive treatment.

- Study population /Sample size

370 subjects aged 12 to 68 with Class III, IV or V LN were enrolled. This included 24 patients (6.5%) below age of 18. The overall sample size was predicted to provide a 90% power to detect a 15% difference between the groups, with a 0.05 level of significance, based upon an assumed response rate of 70%. The number of paediatric patients enrolled was insufficient to detect a difference between groups.

Subjects met American College of Rheumatology criteria for a diagnosis of SLE. Active or active/chronic LN (International Society of Nephrology/Renal Pathology Society 2003 Class III, IV-S or IV-G, V, III+V or IV+V) was confirmed by kidney biopsy within 6 months before randomisation. Subjects also had laboratory evidence of active nephritis at screening, defined as:

*Class IV-S or IV-G*

- proteinuria ≥1000 mg/24 h, or
- serum creatinine above 1.3 mg/dL (115 µmol/L), or
- active urinary sediment: any of >5 WBC/hpf, >5 RBC/hpf, 2+ or more on dipstick, or red cell casts in the absence of infection or other causes

*Class III or V*

- proteinuria ≥2000 mg/24 h, or
- serum creatinine above 1.3 mg/dL (115 µmol/L)

- Treatments

Paediatric patients were treated according to the adult schedule. Dosage reductions were permitted for subjects weighing less than 50kg.

Oral MMF was given BID, titrated from 0.5 g BID in Week 1 and 1.0 g BID in Week 2 to a target dose of 3.0 g/day in Week 3. Reduction was permitted to 2.0 g/day in response to AEs. Dosing was in the form of 500mg oral tablets.

IVC was given in monthly pulses of 0.5-1.0 g/m2, according to the modified National Institutes of Health protocol.

Both groups received prednisone, with a defined taper from a maximum starting dose of 60 mg/day.

- Outcomes/endpoints

The primary efficacy parameter for the induction phase was the number and percentage of subjects showing treatment response at 24 weeks, as adjudicated by the Clinical Endpoints Committee (CEC).

Treatment response was defined as:

(a) Decrease in proteinuria, defined as decrease in the urine protein/creatinine ratio to <3 in subjects with baseline nephrotic range proteinuria (≥3 urine protein/creatinine ratio) or decrease in the urine protein/creatinine ratio by ≥50% in subjects with sub-nephrotic proteinuria (<3 urine protein/creatinine ratio) and

(b) Stabilization of serum creatinine (i.e., a week 24 serum creatinine level ±25% of baseline), or improvement.

There were also a number of secondary endpoints including renal remission, extra-renal remission, BILAG scale, SLICC-DI score, SF-36 score, biochemical and immunological parameters.

- Statistical Methods

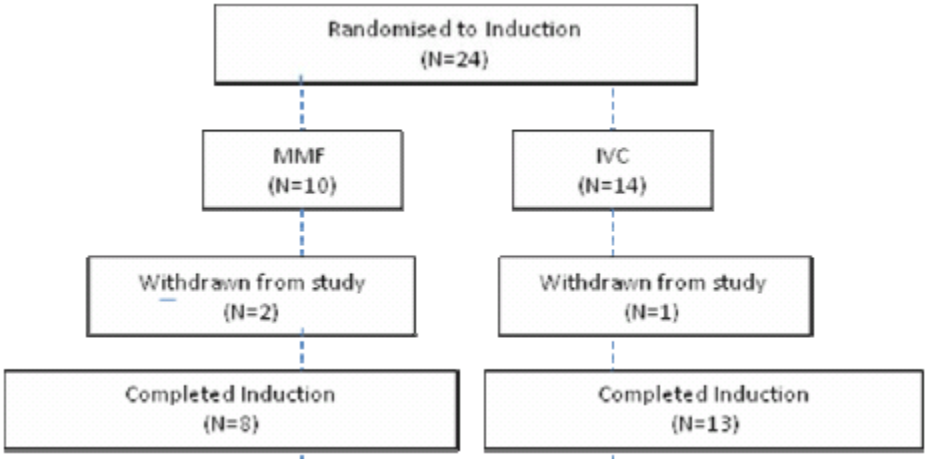
The primary endpoint analyses were performed on the ITT population. Paediatric subjects were analysed separately. Withdrawals were assessed as non-responders.

**Results**

- Recruitment/ Number analysed

At 24 weeks, 21 out of 24 paediatric subjects (87.5%) remained in the study. 2 subjects in the MMF group and one in the IVC group withdrew. This withdrawal rate was consistent with the overall study population.

Disposition of paediatric subjects in the induction phase is shown below:




- Baseline data

Of the 24 paediatric patients (aged 12-18) randomised, 19 were female and 5 were male. Median age was 15 years. The median duration of LN was 1 year in both groups (range 1-3 years). Paediatric patients were less likely to have a nephrotic-range proteinuria than adult patients.

- Efficacy results

In the overall population there was no significant difference in the proportions of subjects meeting the response criteria between the MMF (56.2%) or IVC (53%) groups (p=0.575; OR 1.2; 95% CI for OR 0.8-1.8).

Of the 10 paediatric subjects randomised to receive MMF, 7 subjects (70%) were classified as responders at 6 months, compared to 8/14 responders (57.1%) among those receiving IVC. This difference did not achieve statistical significance (p=0.527; OR 2.0; 95% CI for OR 0.2-15.5).

- Safety results

In the LN clinical program, in Study WX17801, 245 subjects received treatment with MMF of which 184 subjects received MMF at doses up to 3 g daily for up to 24 weeks during the induction phase.

*Overall induction population*

The majority of subjects (96.2% MMF and 95.0% IVC) reported at least 1 AE during induction treatment, with 13.0% of MMF-treated subjects and 7.2% of IVC-treated subjects being withdrawn due to AEs. The most common treatment-emergent AEs, reported in approximately two-thirds of all subjects, were infections and infestations. There were 9 deaths in the MMF group (4.5%) and 5 in the IVC group (2.8%). Infection was either considered the cause of death or was temporally associated with events leading to death in all but 1 of the 9 MMF-treated subjects and in 2 of the 5 IVC-treated subjects.

There were a total of 157 serious adverse events (SAEs) in 92 subjects reported across the 2 treatment groups in the overall study population during the induction phase. The total number of SAEs was similar across treatment groups; however, a larger proportion of subjects reported SAEs in the MMF treatment group compared with the IVC group. As with the AEs, the largest proportion of SAEs was in the infections and infestations system organ class for both treatment groups. The incidence of infections and infestations SAEs was similar across treatment groups.

*Paediatric induction population*

Ten paediatric subjects received MMF in the induction phase.

During the induction phase, 3/14 (21.4%) on IVC compared to 3/10 (30%) on MMF developed serious infections. The 3 MMF cases were 2 cases of pneumonia and one case of meningococcal meningitis: one 16 year old female died of an apparent pulmonary infection. The 3 IVC cases were pneumonia, bronchitis and an unspecified respiratory infection. 40% of paediatric MMF patients reported SAEs, compared to 35.7% for IVC, most commonly infections and infestations. The corresponding proportions in the adult groups were 27.0% and 21.7%.

**Maintenance phase**

**Methods**

- Objective(s)

The primary efficacy objective for the maintenance phase was to demonstrate the superiority of MMF therapy compared to AZA in maintaining remission and renal function in patients with lupus nephritis.

- Study design

The maintenance phase was a randomised double-blind parallel group study. Subjects that were assessed to have achieved a protocol-defined response, after 24 weeks of induction treatment, were re-randomised (1:1) to maintenance treatment with either MMF or AZA.

Response was defined as:

(a) Decrease in proteinuria, defined as decrease in the urine protein/creatinine ratio to <3 in subjects with baseline nephrotic range proteinuria (≥3 urine protein/creatinine ratio) or decrease in the urine protein/creatinine ratio by ≥50% in subjects with sub-nephrotic proteinuria (<3 urine protein/creatinine ratio). This ratio is based on the 24 hour urine collection.

and

(b) Stabilization of serum creatinine (i.e., at 24 weeks serum creatinine level ±25% of baseline), or improvement.

Subjects who achieve complete (renal) remission at the end of the induction phase were also eligible to enter the maintenance phase. Complete (renal) remission was defined as: return to normal serum creatinine, proteinuria ≤ 500mg/24 hours, and inactive urinary sediment.

Randomisation was stratified according to race/ethnicity, biopsy class and induction phase treatment.

- Study population /Sample size

227 subjects aged 12 to 64 who, in the opinion of the investigator, had achieved a clinical response to induction therapy, were enrolled.

- Treatments

Paediatric patients were treated according to the adult schedule. Dosage reductions were permitted for tolerability and for subjects weighing less than 50kg.

Treatments were administered in a double-blind double-dummy fashion:

MMF 2.0 g/day as 500mg tablets

AZA 2.0 mg/kg/day as 50mg capsules (rounded up or down to nearest 50mg)

Subjects on MMF during the induction phase started maintenance treatment at 2.0 g/day of MMF/matching placebo, whereas subjects on IVC during the induction phase started maintenance treatment at 1.0 g/day MMF/matching placebo for the first week, followed by an increase to 2.0 g/day for the second and subsequent weeks. Dosing of maintenance medication was not started until 3 weeks after the last IVC dose.

Subjects were allowed to be treated with prednisone or an equivalent dose of another corticosteroid at a maximum dose of 10 mg per day, with dose reduction per investigators' judgment.

- Outcomes/endpoints

The primary analysis compared the time to treatment failure in each of the treatment arms for the intent to treat (ITT) population. Treatment failure was defined as the first occurrence of any of the following events: death, ESRD, sustained doubling of serum creatinine, renal flare (proteinuric and/or nephritic) or the requirement for rescue therapy for exacerbation or deterioration of LN as adjudicated by a blinded CEC. Subjects were treated in the maintenance phase for up to 36 months.

There were also a number of relevant secondary endpoints including renal remission, extra-renal remission, BILAG score, SLICC/ACR score, SF-36 score, biochemical and immunological parameters.

- Statistical Methods

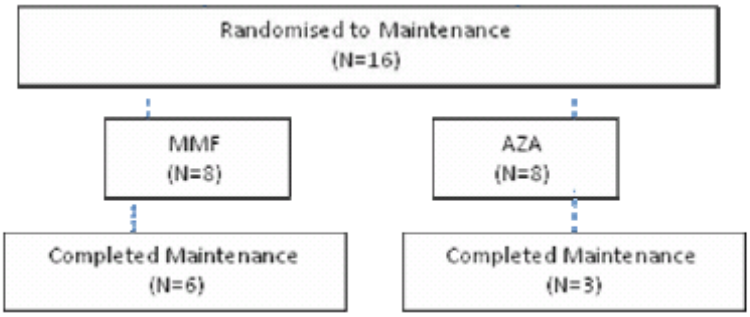
The primary endpoint analyses were performed on the ITT population. Paediatric subjects were analysed separately because of the uniqueness of the population being studied.

**Results**

- Recruitment/ Number analysed

Sixteen of the 24 paediatric subjects (age <18 years) enrolled into the induction phase of Study WX17801 subsequently entered the maintenance phase. Of these, 8 received MMF and 8 received AZA as maintenance therapy.

Disposition of paediatric subjects in the maintenance phase is shown below:




- Baseline data

Thirteen of the paediatric subjects were female and 3 were male, with a median age of 14 (range 12-16).

- Efficacy results

In the overall population, MMF achieved the primary endpoint of statistical superiority to AZA, for time to treatment failure (p=0.003; HR (95% CI) 0.44 (0.25-0.77)) - see figure 1:

**Fig. 1: Kaplan-Meier Curve of Time to Treatment Failure by Time Interval (Intent to Treat Population)**

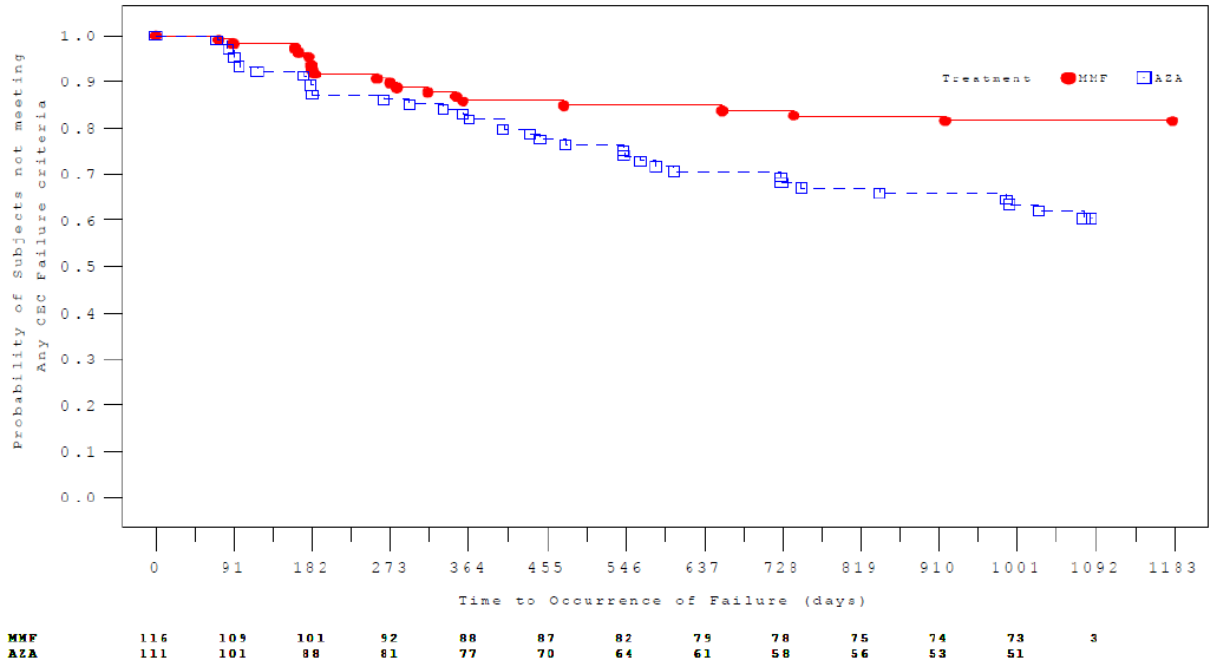



Table 1 compares the withdrawals and treatment failures during the maintenance phase:

**Table 1: Study WX17801 Maintenance: Withdrawals and treatment failures**

| | Adolescents (Age <18 Years) | | Adults (Age ≥18 Years) | |
|---|---|---|---|---|
| | MMF (N=8) | AZA (N=8) | MMF (N=108) | AZA (N=103) |
| Completed 36-month maintenance phase | 6 (75.0) | 3 (37.5) | 67 (62.0) | 51 (48.5) |
| Withdrawn from maintenance phase | 2 (25.0) | 5 (62.5) | 41 (38.0) | 52 (50.5) |
| **Primary Endpoint** | | | | |
| Treatment failure | 1 (12.2) | 5 (62.5) | 18 (16.7) | 30 (29.1) |
| **Primary Endpoint Criteria Met**[1] | | | | |
| Death | 0 | 0 | 0 | 1 (1.0) |
| ESRD | 0 | 2 (25.0) | 0 | 1 (1.0) |
| Doubling serum creatinine | 0 | 1 (12.5) | 1 (0.9) | 4 (3.9) |
| Renal flare | 1 (12.5) | 5 (62.5) | 14 (13.0) | 20 (19.4) |
| Rescue for LN | 0 | 3 (37.5) | 10 (9.3) | 17 (16.5) |

[1] Subjects can meet primary endpoint on >1 criteria.

Notes: AZA = azathioprine; ESRD = end stage renal disease; LN = lupus nephritis; MMF = mycophenolate mofetil.

In the paediatric population, the rates of treatment failure over 36 months were 12.5% for MMF (1/8) compared to 62.5% for AZA (5/8). The single treatment failure in the MMF group was a renal flare (a second patient was withdrawn due to AE). In the AZA group, 5 were withdrawn for the maintenance

phase, all treatment failures, of which 2 were ESRD. The paediatric withdrawal rate was similar to the overall population.

- Safety results

115 subjects received MMF at doses up to 2 g daily for up to 36 months in the maintenance phase (54 of these subjects did not receive MMF in the induction phase).

*Overall maintenance population*

At least 1 AE was experienced by most subjects: 98.3% in the MMF group and 97.3% in the AZA group. Infections and infestations were the most commonly reported AE: 79.1% in the MMF group and 78.4% in the AZA group. Discontinuation due to an AE occurred in 25.2% of MMF patients and 39.6% of AZA patients. Leucopenia resulted in treatment withdrawal in 2.6% and 9.0% of MMF- and AZA-treated subjects respectively.

Fewer MMF subjects had an SAE (23.5% MMF, 33.3% AZA). The most frequent SAEs were infections and infestations (9.6% MMF, 11.7% AZA). In the maintenance phase, no infections resulted in death.

*Paediatric maintenance population*

8 paediatric subjects received MMF for up to 36 months in the maintenance phase (6 of these subjects were previously treated with IVC during induction).

All paediatric patients reported at least one AE. Infections and infestations were the most commonly reported AEs in both treatment groups: 7/8 on MMF (87.5%) and 6 out of 8 on AZA (75%). The majority were non-specific upper respiratory infections. Two of the infections in paediatric subjects receiving MMF required IV antibiotics: 1 pneumonia and 1 skin abscess.

Ultimately 2 paediatric subjects receiving MMF withdrew from the maintenance phase as a result of an AE (1 lupus flare, 1 infection). Five paediatric subjects receiving AZA withdrew, including 1 with leukopenia and 4 with a lupus flare.

Two paediatric subjects receiving MMF (25%) developed 3 SAEs: 1 episode of pneumonia, 1 skin abscess, and 1 SLE flare. Four paediatric subjects receiving AZA (50%) developed 6 SAEs, 1 pneumonia, 1 abdominal pain, 1 thrombosis, and 3 SLE flares.

### 3. Discussion on clinical aspects

The primary efficacy objective of the induction phase, a demonstration of superiority over IVC, was not met, although the majority of IVC and MMF subjects responded to therapy (53.0% IVC, 56.2% MMF). During the maintenance phase, for the overall population, MMF demonstrated statistically significant superiority to AZA, for time to treatment failure. The efficacy results in paediatric subjects were consistent with the overall population in both the induction and maintenance phases of the study. The number of paediatric subjects was small, therefore further statistical analysis was not warranted.

Infections and infestations were the most commonly reported AEs in both adult and paediatric subjects. This is consistent with the known safety profiles of MMF, IVC and AZA. In the induction phase, there was an excess of deaths associated with MMF compared to IVC in the overall population. In the maintenance phase, there were less SAEs and fewer AEs leading to discontinuation in the MMF group compared to the AZA group. The safety outcomes in paediatric patients were similar to the overall population.

## Rapporteur's overall conclusion and recommendation

**Overall conclusion**

The MAH has provided an adequate overview of data from the paediatric subsets of Study WX17801. The number of paediatric patients included is small and therefore it is not possible to conclude regarding the efficacy of mycophenolate mofetil in the treatment of lupus nephritis in children aged 12-18, based on this study. There is currently no approved indication for CellCept in the treatment of lupus nephritis for any age range. The paediatric safety data presented does not raise any new safety concerns.

It is agreed with the MAH that no regulatory action is required as a result of this Article 46 submission.

**Recommendation**

☒ **Fulfilled** –

No regulatory action required

☐ **Not fulfilled**:

# Additional clarifications requested

Not applicable.