# Cost-effectiveness of targeted-release form (TRF)-budesonide for the treatment of adult population with immunoglobulin A nephropathy (IgAN) in Greece

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## Introduction

- Immunoglobulin A nephropathy (IgAN) is a kidney disease that leads to end-stage renal disease (ESRD) in almost half of all patients within 20 years of diagnosis (1). ESRD is the result of inflammation triggered by the accumulation of IgA protein deposits (2).
- Real-world evidence from a national registry of rare kidney diseases (UK RaDaR) indicates that higher levels of proteinuria are associated with worse 10-year kidney survival (3).
- Current management of primary IgAN in patients at risk of developing kidney failure typically comprises of blood pressure management to reduce stress on the kidneys (4). As the disease progresses to ESRD, kidney dialysis and kidney transplantation may be needed (4).
- The use of corticosteroids may lead to adverse events (AEs) and their administration is recommended only for IgAN patients at risk of rapid progression to ESRD and for limited duration (5). Moreover, the addition of immunosuppressive therapy to intensive supportive care does not improve outcomes substantially while it is accompanied with increased frequency of AEs (6).
- The targeted-release formulation of budesonide (TRF-budesonide) is a novel, oral formulation of the glucocorticoid budesonide, licensed in Europe for patients with primary IgAN who have at least 1 g of protein in their urine per day or a urine protein-to-creatinine ratio (UPCR) of at least 0.8 g/ (7) The TRF-budesonide is designed to target a primary site of IgAN, in the mucosal layer of the intestine.

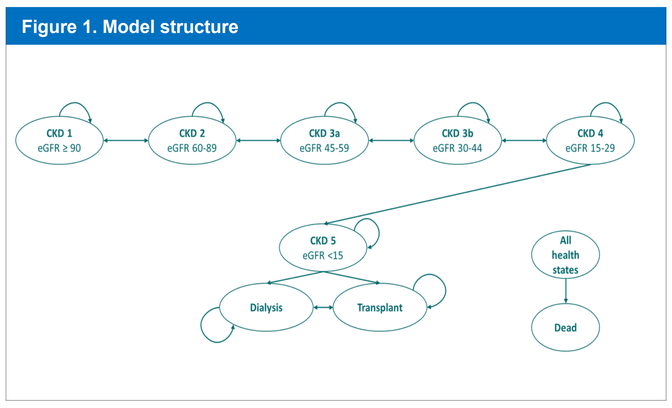
## Objective

- This study aims to assess the cost-utility of TRF-budesonide in patients with primary IgAN at risk of rapid disease progression with UPCR ≥0.8 g/g compared to standard of care (SoC) in Greece.

## Methods

- A global cost-effectiveness cohort-level was adapted to compare TRF-budesonide with SoC from the perspective of the Greek public payer (EOPYY), over a lifetime, with monthly cycles and applying 3.5% discount rate on cost and health outcomes.
  - The model's health states were mostly defined by chronic kidney disease (CKD) stage, defined by estimated Glomerular Filtrate rate (eGFR) levels (Figure 1).
  - Health outcomes are captured by each health state representing a category of complications that occur in IgAN.
  - Within each health state there is a series of possible events, whereby the distribution of these events contributes to the costs associated with the respective health state.
- TRF-budesonide is assumed to be provided to patients as a 120-tablet (30-day) pack and to be used alongside current SoC.
- SoC consists of angiotensin converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs) and sodium-glucose cotransporter 2 inhibitor (SGLT2i), according to Greek clinical experts;
- A structured resource use questionnaire was developed to validate global data where necessary and to assess local inputs from three Greek clinical experts on nephrology.
- Health outcomes were expressed in quality-adjusted-life-years (QALYs), whereas costs were expressed in euros, 2024 values (€, 2024)
- Cost parameters included: drug acquisition cost, health state costs, management of AEs and end-of-life cost.
- The base-case cost utility analysis, the incremental costs and incremental QALYs were assessed to calculate the incremental cost-effectiveness ratio (ICER).
- Scenario analyses with different time horizons, discount rates, sources from utilities, dose reduction and assumptions were explored.
- In order to account for first-order uncertainty around the data used for input parameter values, a one-way deterministic sensitivity analysis (DSA) was performed. The parameters varied by 20% to derive the upper and lower values. A tornado graph was generated (Figure 2).
- Probabilistic sensitivity analysis (PSA) was performed to explore uncertainty in the results with 1,000 iterations and the cost-effectiveness plane & cost-effectiveness acceptability curve were generated (Figure 3, Figure 4).

**Figure 1. Model structure**




Note: The arrows represent the permitted transitions between health states. eGFR measured as 35mL/min/1.73m2

**Table 1. Baseline patient characteristics**

| Parameter | Mean | Source |
|---|---|---|
| Age | 42.7 years (SD=10.76) | |
| Proportion female | 34.1% | NefIgArd Part B data (8) |
| Average weight | 84.5 kg (SD=18.99) | |
| **Model baseline distribution across CKD states** | | |
| CKD stage 1 | 2.6% | |
| CKD stage 2 | 34.2% | |
| CKD stage 3a | 39.5% | NefIgArd Part A data (9) |
| CKD stage 3b | 23.7% | |
| CKD 4 | 0.0% | |
| **Total** | **100%** | |

## Model Inputs

- **Patient characteristics** In line with the marketing authorization of European Medicines Agency (EMA) (7), the patient population for the economic analysis consists of adults (≥18 years old) with IgAN, who have at least 1 g of protein in their urine per day or a UPCR of at least 0.8 g/g. Patient characteristics used in the model were derived from the NefIgArd Nef-301 Part B study (8).
- **Baseline patient distribution** across CKD stages was derived from NefIgArd Nef-301 Part A study (9) (Table 1). A scenario with data from Greek clinical experts was explored.
- **Clinical inputs:** Data from NefIgArd Nef-301 was used to inform transition probabilities from baseline to 24 months (9).
  - eGFR values were mapped to CKD stages at baseline and after 24-months from receiving initial treatment. Patients are considered to have 'transitioned' if they were in a different CKD stage after 24 months of treatment compared with baseline, with the likelihood of transitioning evaluated by treatment arm and baseline CKD stage (Table 2).
  - Transition probabilities in TRF-budesonide arm in retreated patients follow the TRF-budesonide transition probabilities of the period 0-24 month (Table 2) adjusted for a 90% waning effect.
  - Transition probabilities in TRF-budesonide arm beyond the 24th month were assumed equivalent to the observed transition probabilities in the NefIgArd Nef-301 SoC arm (9).
- **All treatment-related AEs** occurring in ≥4% of patients in either treatment arm of the safety analysis set of the NefIgArdNef-301 clinical study report (CSR) pooled dataset were included in the model (9). Treatment-emergent severe adverse events (TEAEs) were also included.
- **HRQoL:** EQ-5D-5L data were sourced from literature (10, 11) to inform patient utility assumptions, since no HRQoL data were collected during the NefIgArd Nef-301 trial.
- **AE disutilites** were obtained from a targeted literature review (12).
- **Mortality:** Data from UK RaDaR were used to inform the risk of mortality for CKD stages 1–5, transplant, and dialysis (3). Life tables for Greece were used for background mortality, adjusted for age and sex (13).
- **Cost inputs:** Healthcare resource use was informed by Greek clinical experts in nephrology. It was combined with unit costs to assess the annual health state costs (Table 4).
  - The dosing schemes of TRF-budesonide and SoC were based on their Summary of Product Characteristics (SPCs).
  - Treatment with TRF-budesonide lasts 9 month, followed by a reduced dose interval for 2 weeks period.
  - One round of retreatment wand a tapered dose period for another 2 weeks (see Table 4 for dosage scheme in each treatment as assumed in the analysis for the 65.7% of TRF-budesonide patients (aligned with NefIgArd trial & Greek clinical experts).
  - The repartition of drug repartition of SoC: ACEis: 48%, ARBs: 52% and SGLT2i: 77%, based on clinical experts (Table 4).
  - *Drug acquisition costs* were based on ex-factory prices accounting for all relevant legal discounts. Ex-factory prices were published in the drug price bulletins from the Ministry of health and positive reimbursement list (14,15,16).
  - *Reimbursement costs for medical exams* were sourced from EOPYY website (17).
  - *The Greek catalogue of Diagnosis Related Group* (Gr-DRG) was used to calculate any hospitalization costs in CKD stages (18).
  - *AE costs* were derived from literature and were applied to the AE rates from NefIgArd trial (9).
  - *End-of life (EoL) costs:* EoL care is mostly managed at inpatient setting (clinical experts opinion). Its cost was estimated at €1,960.64 (DRG code used: L60C) (18).

**Table 2. Transition probabilities in both treatment arms up to 24 months**

| From / To | CKD 1 | CKD 2 | CKD 3a | CKD 3b | CKD 4 |
|---|---|---|---|---|---|
| **TRF-budesonide transition probabilities** | | | | | |
| CKD 1 | 95.09% | 4.91% | | | |
| CKD 2 | 0.36% | 98.32% | 1.31% | | |
| CKD 3a | | 0.37% | 97.12% | 2.51% | |
| CKD 3b | | | 0.63% | 97.77% | 1.59% |
| CKD 4 | | | | 0.63% | 99.37% |
| **SoC transition probabilities** | | | | | |
| CKD 1 | 92.85% | 7.15% | | | |
| CKD 2 | 0.20% | 97.42% | 2.39% | | |
| CKD 3a | | 0.20% | 95.65% | 4.15% | |
| CKD 3b | | | 0.35% | 96.83% | 2.82% |
| CKD 4 | | | | 0.35% | 99.65% |
| **Transition probabilities: From CKD 5, Dialysis and Transplant (both in TRF-budesonide & SoC arm)** | | | | | |
| | CKD 5 | Dialysis | Transplant | | |
| CKD 5 | 95.30% | 4.50% | 0.20% | | |
| Dialysis | 99.50% | 0.50% | | | |
| Transplant | 0.70% | 99.30% | | | |

**Table 3. Base case utility values**

| Health state | Mean value (SE) | Reference |
|---|---|---|
| CKD 1 | 0.90 (0.04) | (10) |
| CKD 2 | 0.90 (0.04) | |
| CKD 3a | 0.87 (0.03) | |
| CKD 3b | 0.87 (0.03) | |
| CKD 4 | 0.85 (0.03) | |
| CKD 5 | 0.85 (0.05) | |
| Haemodialysis | 0.44 (0.03) | (11) |
| Peritoneal dialysis | 0.53 (0.07) | |
| Post transplant | 0.71 (0.02) | |

Note: Standard error calculation: (1-mean)/(1.96*2)

**Table 4. Drug Treatment costs (€, 2024)**

| TRF - budesonide Dose description | Dose per cycle* | Packs per cycle* | Treatment cost per cycle* |
|---|---|---|---|
| Treatment period | | | |
| 16mg OD for 9 months | 487 mg | 1.01 | € 5,721.61 |
| Reduced dose period (in month 10) | | | |
| 8 mg OD for 2 weeks | 112 mg | 0.23 | € 1,315.85 |
| Tapered dose period | | | |
| 4mg OD for 2 weeks | 56 mg | 0.12 | € 657.93 |

| SOC | Weighting | Monthly cost | Weighted average cost |
|---|---|---|---|
| ACEi | 42% | € 9.15 | € 7.63 |
| ARB | 58% | € 6.55 | |
| SGLT2i | 77% | € 47.03 | € 36.05 |
| **Weighted average cost of SoC** | | | **€ 43.69** |

Note: SoC drugs weights source: (Greek clinical experts); drug costs source: (14,15,16)

## Results

- TRF-budesonide would result in €38,566 additional costs and 0.473 additional QALYs compared to SoC alone, resulting in an ICER of €81,537 per QALY gained.
- DSA revealed that the health state utilities are the parameters that highly would affect the basecase results.
- PSA confirms the robustness of the base case results and illustrates that at willingness-to-pay thresholds (WTP) >€90,000, which is an acceptable WTP for drugs designated as orphan (21) TRF-budesonide is most likely to be the cost-effective treatment option vs. SoC.

**Table 6. base case results of TRF-budesonide vs SoC**

| Arm | Total Costs | Total QALYs | Incremental Costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| **TRF-budesonide** | € 327,129 | 16.089 | | | |
| **SoC** | € 288,563 | 15.616 | € 38,566 | 0.473 | € 81,537 |

**Table 5. Medical resource use costs per cycle by health state**

| Health state | Total cost per cycle | Description/ Source |
|---|---|---|
| CKD 1 | € 4.30 | EOPYY reimbursed medical exams (17) |
| CKD 2 | € 6.02 | |
| CKD 3a | € 12.55 | |
| CKD 3b | € 15.01 | |
| CKD 4 | € 26.43 | |
| CKD 5 | € 37.61 | |
| Dialysis | € 3,254.59 | Cost of hemodialysis (19) & transportation cost (20) |
| Transplantation cost (pre-assessment & procedure) | € 11,954.77 † | DRG code: A64Z, A17B (20) |
| Transplantation maintenance | € 514.74 | a) Nephrologist visits & blood tests every four months (17)<br>b) Tacrolimus 0.25mg/kg / day (14)<br>c) Hospitalization once per year for 60% of patients undergone kidney transplantation (20) |

Note: †one –off upon the transition to the transplant health state

**Figure 2. Tornado graph vs. SoC**

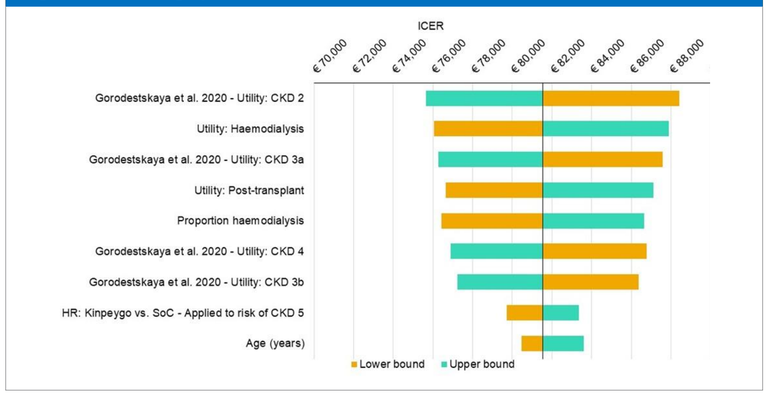



**Figure 3. CE plane (1,000 iterations)**

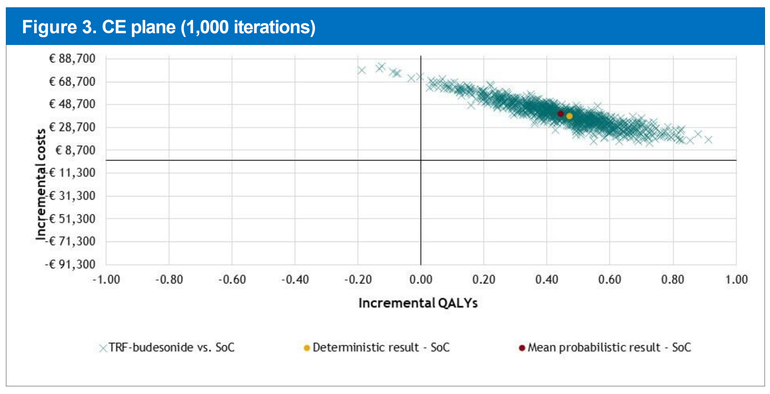
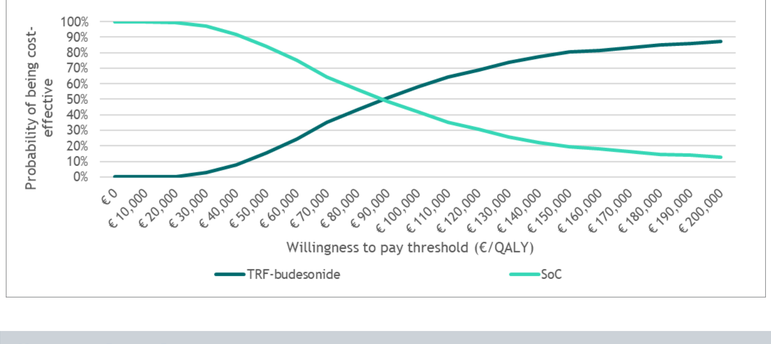



**Figure 3. cost-effectiveness acceptability curve**




## Conclusion

- TRF-budesonide would provide a cost-effective option for a patient population with a high unmet need in Greece.

**Abbreviations**: ACEi: angiotensin converting enzyme inhibitor, AE: adverse events, ARB: angiotensin receptor blocker CE: cost-effectiveness, CKD: chronic kidney disease, DRG: diagnosis related group, DSA: deterministic sensitivity analysis, eGFR: estimated Glomerular Filtration Rate, EQ-5D: European Quality of Life 5 Dimensions, ERT: Enzyme replacement therapies, ESRD: End stage Renal Disease, GP: general practitioner, HR: hazard ratio, HRQoL: health related quality of life, ICER: incremental cost- effectiveness ratio, IgAN: Immunoglobulin A Nephropathy, MoH: ministry of health,OD: once daily, PSA: Probabilistic sensitivity analyses, Q4: fourth trimester, QALYs: quality adjusted life years, SE: standard error, SGLT2i: sodium-glucose cotransporter 2 inhibitor, SoC: standard of care, TRF -budesonide: targeted release formulation of budesonide, UPCR: urine protein-to-creatinine ratio, WHO: world health organization, WTP: willingness to pay.

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