# NHS England Evidence Review:

Delayed-release mercaptamine bitartrate (cysteamine) for the treatment of nephropathic cystinosis

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Delayed-release mercaptamine bitartrate (cysteamine) for the treatment of nephropathic cystinosis

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

# Contents

# 1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of delayed-release (DR) mercaptamine bitartrate (cysteamine) compared to current standard care in the treatment of nephropathic cystinosis.

Nephropathic cystinosis is a life-long condition and is generally diagnosed in early childhood, usually before the age of two years. This condition reduces life-expectancy and is associated with significant morbidity throughout childhood and adult life due to the development of renal and extra-renal complications.

The population covered by this review is people of all ages with confirmed nephropathic cystinosis.

Current standard care for nephropathic cystinosis is immediate-release (IR) mercaptamine bitartrate, sometimes referred to as short-acting (SA) mercaptamine bitartrate. This acts to reduce cystine accumulation in cells, and when started early, it delays the development of renal failure and other complications. This needs to be taken with food every six hours. The proposed intervention is DR mercaptamine bitartrate, which can be taken every 12 hours. This 12 hourly dosing would remove the need for patients to wake up in the middle of the night to take medication and stop the need for school aged children to be taking medication in the school day.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from DR mercaptamine bitartrate more than others.

## 2. Executive summary of the review

This review examined the clinical effectiveness, safety and cost effectiveness of delayed-release (DR) mercaptamine bitartrate (cysteamine) compared to current standard care in people of all ages with nephropathic cystinosis. The searches for evidence published since 01 January 2012 were conducted on 26 March 2024 and identified 43 references. The titles and abstracts were screened, and 33 full text papers were obtained and assessed for relevance.

Four papers were identified for inclusion in this review; one paper was a three week crossover RCT (Langman et al 2012),[1] one paper was a prospective single-arm follow-up study (Langman et al 2014) to the crossover RCT, one paper was a prospective cohort study (Gaillard et al 2021), and one paper was a prospective case series (Vaisbich et al 2022).

The three week crossover RCT (Langman et al 2012) compared DR cysteamine bitartrate versus immediate-release (IR) cysteamine bitartrate in patients with nephropathic cystinosis; outcomes were reported after each three week treatment period. The prospective single-arm follow-up study (Langman et al 2014) included 40 of the 41 patients who completed the crossover RCT, and reported comparative evidence for quality of life, comparing scores during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine during the follow-up study. This prospective single-arm follow-up study also reported non-comparative evidence for quality of life measures and for the remaining outcomes (i.e. disease response, progression of cystinosis associated renal disease, growth measurements, and safety) after two years of DR cysteamine bitartrate treatment. The population in these two related studies included mainly children and adolescents aged 21 years or less.

One prospective cohort study (Gaillard et al 2021) provided evidence on 17 patients with nephropathic cystinosis (median age 13.9 years; range 5.4 to 33 years). Four of the included patients were receiving short-acting (SA) cysteamine at study inclusion and for up to 13 weeks, but then switched to DR cysteamine for the remainder of the 12 months study duration.[2] The other 13 patients received DR cysteamine throughout the whole study duration. Outcomes were reported at 12 months follow-up, using objective measures to compare adherence to treatment with DR cysteamine versus SA cysteamine. The remaining outcomes (i.e. disease response, self-reported adherence, progression of cystinosis associated renal disease) were reported as non-comparative evidence for all patients (i.e. including the four patients who were initially receiving SA cysteamine and then switched to DR cysteamine). One prospective case series (Vaisbich et al 2022) provided non-comparative evidence on 15 treatment naïve children under the age of six years with nephropathic cystinosis who were treated with DR cysteamine. Outcomes were reported at interim timepoints up to 18 months follow-up and/or at study exit (timeframe not clear)[3].

The included papers were published between 2012 and 2022. One study was conducted in France, one in the USA and Brazil, and the two papers related to the crossover RCT were conducted in the USA, France and the Netherlands. No evidence was identified for the important outcomes activities of daily living (ADLs) or progression of non-renal cystinosis associated disease. No evidence relating to cost effectiveness was identified.

[1] An additional paper (Anonymous 2013) was identified as an erratum to the crossover RCT (Langman et al 2012) and provided a correction to the data collected, which was stated not to have affected the overall findings reported in the RCT.
[2] The authors stated that the four patients who received SA cysteamine at study inclusion switched to DR cysteamine mainly due to participation in a trial that administered DR cysteamine.
[3] Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.

Mercaptamine bitartrate is described differently across varying countries; the papers included in this review report on delayed-release (DR) cysteamine/cysteamine bitartrate (RP103 or Procysbi) or immediate-release (IR) or short-acting (SA) cysteamine/cysteamine bitartrate (Cystagon). For the purposes of this review, the terms referred to in the individual papers are used when referring to an individual paper, and DR or IR mercaptamine bitartrate are used when referring to a group of studies or when summarising the results for an outcome.

**In terms of clinical effectiveness:**

**Critical outcomes**

- **Disease response**
  - *DR mercaptamine bitartrate vs IR mercaptamine bitartrate:*

    One three week crossover RCT provided low certainty evidence that mean white blood cell (WBC) cystine levels remained optimal (i.e. ≤1 nmol hemicystine/mg protein)[4] in patients when they were treated with DR cysteamine bitartrate and when they were treated with IR cysteamine bitartrate although three patients treated with IR cysteamine bitartrate had a mean WBC cystine level >2 nmol hemicystine/mg protein and were considered *"not well controlled"*. There was a statistically significant difference between treatment groups which indicated greater benefit with DR cysteamine bitartrate.
  - *DR mercaptamine bitartrate vs no comparator:*

    One prospective cohort study, one prospective case series, and one prospective single-arm follow-up study provided very low certainty evidence showing mixed findings. The prospective cohort study showed that WBC/leukocyte cystine levels increased from baseline to 12 months follow-up, with the median follow-up results being greater than the optimal target of ≤1 nmol hemicystine/mg protein, but no statistical measures were reported. The prospective case series reported a *"clinically meaningful"* decrease (i.e. improvement) in WBC cystine levels from baseline to study exit (timeframe not clear),[5] although the definition of a clinically meaningful effect size was not provided. The prospective single-arm follow-up study reported that WBC cystine levels *"were maintained under optimal control (<1 nmol hemicystine/mg protein)"* from baseline to 24 months follow-up.

    These three studies also reported that WBC/leukocyte cystine levels were optimal (i.e. ≤1 nmol hemicystine/mg protein) at follow-up for a median of 60% of visits for each patient, or for 76.9% or 100% of patients, respectively.
- **Treatment adherence**
  - *DR mercaptamine bitartrate vs IR mercaptamine bitartrate:*

    One prospective cohort study provided very low certainty evidence showing greater adherence to treatment (scored using objective measures)[6] at 12 months follow-up when patients were treated with DR cysteamine compared to the four patients initially treated with SA cysteamine, but no statistical measures were reported.
  - *DR mercaptamine bitartrate vs no comparator:*

[4] The PICO document states that the target white cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.
[5] Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.
[6] Electronic caps (MEMs®) were adapted to existing bottles of cysteamine. Electronic monitoring is a method for compiling drug dosing histories, integrating a small microcircuit into drug packages and recording the time and date (i.e. opening) whenever it detects that a dose of drug is removed from the bottle.

One prospective cohort study provided very low certainty evidence showing high self-reported adherence (scored using subjective measures)[7] at 12 months in patients with nephropathic cystinosis treated with DR cysteamine.

- **Progression of cystinosis associated renal disease**
  - *DR mercaptamine bitartrate vs IR mercaptamine bitartrate:*

    No evidence was identified for progression of cystinosis associated renal disease.
  - *DR mercaptamine bitartrate vs no comparator:*

    One prospective cohort study, one prospective case series, and one prospective single-arm follow-up study provided very low certainty evidence relating to progression of cystinosis associated renal disease in patients with nephropathic cystinosis treated with DR mercaptamine bitartrate. The prospective cohort study reported that *"GFR remained stable over the year in our cohort of patients"*, but no further details were reported. The prospective case series reported an increase (i.e. improvement) in eGFR from baseline to study exit (timeframe not clear), but no statistical measures were reported. The prospective single-arm follow-up study reported that there were no statistically significant differences in eGFR from baseline to 24 months follow-up, although one patient each underwent renal transplant or renal dialysis.

**Important outcomes**

- **Quality of life (QoL)**
  - *DR mercaptamine bitartrate vs IR mercaptamine bitartrate:*

    One prospective single-arm follow-up study provided very low certainty evidence showing a statistically significant improvement in two of four paediatric quality of life subscale scores and the total score in patients with nephropathic cystinosis when comparing scores during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine during the single-arm follow-up study.
  - *DR mercaptamine bitartrate vs no comparator:*

    One prospective single-arm follow-up study provided very low certainty evidence that when patients were treated with DR cysteamine there was no statistically significant change in any of the paediatric quality of life subscale scores or total score from the follow-up study baseline to 24 months follow-up.[8]
- **Growth measurements**
  - *DR mercaptamine bitartrate vs IR mercaptamine bitartrate:*

    No evidence was identified on growth measurements.
  - *DR mercaptamine bitartrate vs no comparator:*

    One prospective case series and one prospective single-arm follow-up study provided very low certainty evidence relating to growth measurements in patients with nephropathic cystinosis treated with DR cysteamine bitartrate. The prospective case series reported a *"clinically meaningful"* increase (i.e. improvement) in height, weight and body surface area (BSA) Z-scores from baseline to study exit (timeframe not clear), but no statistical measures were reported and the definition of a clinically meaningful effect size was not provided. The prospective single-arm follow-up study reported that

[7] Individual average of self-reported adherence over the year. Participants evaluated their adherence answering the following question on a visual analogical scale: *"How do you evaluate your adherence to cysteamine?"* at each study visit; no further details were provided, but we have assumed this was measured using a score of 1 to 10.

[8] The authors stated that *"There was no loss of the significant changes gained in the social, school, and total function parameters and no decline in the other 2 measured parameters (physical and emotional) during the 24-month study"*.

there were no statistically significant differences from baseline to 24 months follow-up in body mass index (BMI) or height Z-score.

- **Activities of daily living (ADLs)**
  - No evidence was identified for this outcome.
- **Progression of non-renal cystinosis associated disease**
  - No evidence was identified for this outcome.

**In terms of safety:**

- *DR mercaptamine bitartrate vs IR mercaptamine bitartrate:*

  One three week crossover RCT provided low certainty evidence showing that a greater number of adverse events (AEs) were experienced when patients were treated with DR cysteamine bitartrate compared to when they were treated with IR cysteamine bitartrate. For the most common AE (gastrointestinal disorders), most were considered to be treatment-related in both treatment arms. No statistical measures were reported.

  The crossover RCT also provided low certainty evidence that a greater number of serious adverse events (SAEs) were experienced during treatment with DR cysteamine bitartrate compared to treatment with IR cysteamine bitartrate, with most considered not to be treatment-related. No statistical measures were reported.
- *DR mercaptamine bitartrate vs no comparator:*

  One prospective single-arm follow-up study and one prospective case series provided very low certainty evidence that all patients experienced at least one AE during treatment with DR cysteamine; it was unclear whether the AEs were treatment-related in the case series, but all AEs were reported to be treatment-related in the single-arm follow-up study.

  The prospective case series proved very low certainty evidence that the majority of patients experienced at least one SAE, including one patient who died, but none were considered to be treatment-related.

**In terms of cost effectiveness:**

- No evidence was identified for cost effectiveness.

**In terms of subgroups:**

- **Patients with nephropathic cystinosis aged ≤11 years vs aged >11 years**
  - One prospective cohort study reported that patients aged ≤11 years experienced a greater percentage of days with a good adherence score[9] compared to patients aged >11 years (median: 89% and 68%, respectively), whichever cysteamine formulation was given (DR or SA). Statistical measures were not reported.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

[9] Adherence to treatment was assessed using objective measures (i.e. electronic caps [MEMs®]).

## Limitations

The three week crossover RCT did not state the sample size calculation or whether this was met and it was therefore unclear whether the study was sufficiently powered, which limits the ability to draw accurate conclusions about the findings. The crossover RCT reported the use of intention-to-treat (ITT) analysis, but two patients who withdrew from the study were not included in the ITT analysis of the primary outcome (disease response), resulting in the analysis not being based on true ITT methods. The effect of this on the findings is likely to be small, but remains unclear. Furthermore, the duration of treatment was short (i.e. three weeks) for each treatment period, and it was unclear whether there was a sufficient washout period between treatments.

There was heterogeneity across the studies in terms of the differing use of concomitant treatments (e.g. use of proton pump inhibitors [PPIs]), and varying treatment durations which ranged from three weeks to two years. In addition, study populations varied, with one study including only patients with their own kidneys who were well controlled on treatment with IR cysteamine (the main uncertainty relates to the serious selection bias due to the inclusion of only patients who were well controlled on treatment), one study including patients already receiving mercaptamine bitartrate and a proportion of patients who had previously undergone kidney transplant or were receiving kidney dialysis at the time of the study, and one study including only treatment naïve patients. The varying results for some of the outcomes may reflect the different populations. For example, greater reductions (i.e. improvements) in WBC cystine levels were reported from baseline to follow-up in children who were previously treatment naïve, while patients who were already being treated with mercaptamine bitartrate and/or were well controlled on this treatment, did not show such large differences from baseline to follow-up.

The certainty in the clinical effectiveness evidence was very low to low for one critical outcome (disease response), and very low for two critical outcomes (treatment adherence and progression of cystinosis associated renal disease). The certainty in the evidence was very low for the important outcomes (quality of life and growth measurements) and for safety. Factors reducing confidence in the outcomes reported include the serious or very serious risk of bias in all the included studies, and serious or very serious indirectness due to the prospective cohort study including patients who were initially receiving SA cysteamine bitartrate and then switched to DR cysteamine bitartrate for the remainder of the study; and the lack of a comparator for most outcomes in three studies. Further limitations include the small numbers of patients included in the studies and unclear study methods. One of the studies included in this evidence review reported some outcomes (disease response and growth measurements) in terms of clinical relevance, although the definition of a clinically meaningful effect size was not provided, and three studies reported the proportion of patients or patient visits for which WBC/leukocyte cystine levels were ≤1 nmol hemicystine/mg protein (i.e. the target level which is considered optimal). Otherwise, minimum clinically important differences (MCIDs) were not reported for the remaining outcomes.

## Conclusion

This review included one three week crossover RCT, one prospective single-arm follow-up study to the crossover RCT, one prospective cohort study, and one prospective case series. No evidence was available for two important outcomes (ADLs and progression of non-renal cystinosis associated disease) and no evidence was available on cost effectiveness.

The three week crossover RCT found a statistically significant benefit in disease response with DR cysteamine bitartrate compared to IR cysteamine bitartrate in patients with nephropathic

cystinosis, but showed a greater number of adverse events (AEs) and serious adverse events (SAE) during treatment with DR cysteamine bitartrate. The evidence provided by the crossover RCT should be considered as low certainty due to very serious risk of bias resulting from lack of details on methodology. Furthermore, the short duration of treatment (i.e. three weeks) for each treatment arm should be taken into consideration, and it was unclear whether there was a sufficient washout period between treatments.

Comparative evidence was also provided in one single-arm follow-up study and one prospective cohort study. The single-arm follow-up study showed statistically significant improvement in two quality of life subscale scores and the total score in patients with nephropathic cystinosis, when comparing scores during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine during the two year single-arm follow-up study. There was no statistically significant difference in any of the quality of life scores from the follow-up study baseline to two years follow-up.

The prospective cohort study showed higher levels of adherence to DR cysteamine treatment at 12 months follow-up compared to initial treatment with SA cysteamine in four patients. The prospective cohort study also reported treatment adherence in subgroups of patients aged 11 years or younger versus patients older than 11 years (whether receiving DR or SA cysteamine), with the findings showing a decline in adherence levels in adolescents and adults (i.e. 11 years and older). Although the evidence on treatment adherence in these subgroups of patients has been presented in this evidence review, the findings do not indicate whether there are any subgroups of patients that may receive greater clinical benefit from DR mercaptamine bitartrate than the wider population of interest. Furthermore, these subgroups do not reflect those specified in the PICO document (i.e. adult versus paediatric population).

The evidence provided by the prospective single-arm follow-up study, prospective cohort study, and prospective case series should be considered as very low certainty due to the lack of a relevant treatment comparison group, small sample sizes (ranging from 15 to 40 patients), and lack of statistical measures for some outcomes. These three studies reported mixed findings on disease response and progression of cystinosis associated renal disease in patients with nephropathic cystinosis treated with DR mercaptamine bitartrate. The mixed results may reflect the difference in study populations (i.e. different renal function at study enrolment) and different treatment durations. Two of these studies also provided mixed findings on growth measurements, and both studies reported that all patients experienced at least one AE during study treatment, with one of these studies also reporting that most patients experienced at least one SAE. Limited findings were reported by one of these studies on quality of life.

# 3. Methodology

## Review questions

The review question(s) for this evidence review are:

1. In people with nephropathic cystinosis what is the clinical effectiveness of delayed-release mercaptamine bitartrate compared to current standard care?
2. In people with nephropathic cystinosis what is the safety of delayed-release mercaptamine bitartrate compared to current standard care?
3. In people with nephropathic cystinosis what is the cost effectiveness of delayed-release mercaptamine bitartrate compared to current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit more from delayed-release mercaptamine bitartrate more than the wider population of interest?

See Appendix A for the full PICO document.

## Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 26 March 2024.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

# 4. Summary of included studies

Four papers were identified for inclusion in this evidence review (Gaillard et al 2021, Langman et al 2012, Langman et al 2014, Vaisbich et al 2022). One three week crossover RCT (Langman et al 2012) assessed the effectiveness and safety of delayed-release (DR) cysteamine bitartrate compared to immediate-release (IR) cysteamine bitartrate in patients with nephropathic cystinosis.[10] A prospective single-arm follow-up study to the crossover RCT (Langman et al 2014) provided long-term outcomes in patients with nephropathic cystinosis treated for two years with DR cysteamine bitartrate. The population in these two related studies included mainly children and adolescents aged 21 years or less. One prospective cohort study (Gaillard et al 2021) provided evidence on 17 patients with nephropathic cystinosis (median age 13.9 years). Four patients were initially receiving short-acting (SA) cysteamine, but then switched to DR cysteamine for most of the study duration.[11] The other 13 patients received DR cysteamine throughout the whole study duration. One prospective case series (Vaisbich et al 2022) provided evidence on 15 children under the age of six years with nephropathic cystinosis who were naïve to DR cysteamine treatment.

No studies were identified that reported activities of daily living (ADLs) or progression of non-renal cystinosis associated disease. No cost effectiveness studies were identified for inclusion in this review.

Mercaptamine bitartrate is described differently across varying countries; the papers included in this review report on DR cysteamine/cysteamine bitartrate (RP103 or Procysbi) or IR or short-acting (SA) cysteamine/cysteamine bitartrate (Cystagon). For the purposes of this review, the terms referred to in the individual papers are used when referring to an individual paper, and DR or IR mercaptamine bitartrate are used when referring to a group of studies or when summarising the results for an outcome.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

**Table 1: Summary of included studies**

| Study | Population | Intervention and comparison | Outcomes reported |
|---|---|---|---|
| Gaillard et al 2021<br>Prospective cohort study (CrYSTobs)<br>France (3 centres) | n=17 patients with confirmed nephropathic cystinosis<br><br>DR cysteamine: n=17 [Including 4 patients who received SA cysteamine at study inclusion but then switched to DR cysteamine after 26 to 91 days]<br>Male: 7 (41.2%)<br>Age (years) [all patients], median (range): 13.9 (5.4 to 33)<br>Subgroups reported: % days with good adherence score | **Intervention**<br>DR cysteamine bitartrate every 12 hours: 25mg or 75mg capsules (median daily dosage per BSA 1.06 (range: 0.56 to 1.42) mg/m$^2$/day)<br><br>**Comparison**<br>SA cysteamine bitartrate every 6 hours: 50mg or 150mg capsules (median daily dosage per BSA 1.29 (range: 0.97 to 1.64) mg/m$^2$/day)<br><br>Ten (59%) patients had received kidney transplant, and 2 (12%) | Follow-up: 12 months<br><br>**Critical outcomes**<br>• Disease response<br>  • WBC cystine levels (nmol hemicystine/mg protein)<br>  • % visits with WBC cystine levels ≤1 nmol hemicystine/mg protein)<br>• Treatment adherence<br>  • Adherence score (score 0: poor to 2: good)<br>  • Self-reported adherence score (VAS)[a] |

[10] An additional paper (Anonymous 2013) was identified as an erratum to the crossover RCT (Langman et al 2012) and provided a correction to the data collected, which was stated not to have affected the overall findings reported in the RCT.
[11] The authors stated that the four patients who received SA cysteamine at study inclusion switched to DR cysteamine mainly due to participation in a trial that administered DR cysteamine.

| Study | Population | Intervention and comparison | Outcomes reported |
|---|---|---|---|
| | ≤11 years old versus >11 years old | were under kidney replacement therapy (haemodialysis) at inclusion. The authors did not report on other concomitant treatments<br><br>Duration of treatment: 12 months | • Progression of cystinosis associated renal disease<br>• eGFR (ml/min/1.73m$^2$) |
| Langman et al 2012<br>3 week crossover RCT<br>Multicentre (3 centres in the USA and 5 in France and the Netherlands) | n=43 patients with confirmed nephropathic cystinosis<br><br>DR cysteamine bitartrate: n=43<br><br>IR cysteamine bitartrate: n=43<br><br>Male: 24 (56%)<br>Age (years)<br>All patients, mean (SD): 11.7 (4.2)<br>Children (aged between 2 and ≤12 years), n: 27<br>Adolescents (aged between 12 and ≤21 years), n: 15<br>Adults (aged >21 years), n: 1<br><br>No relevant subgroups reported | **Intervention**<br>DR cysteamine bitartrate (RP103) every 12 hours: 25mg or 75mg capsules (mean dose not reported)<br><br>**Comparison**<br>IR cysteamine bitartrate (Cystagon) every 6 hours: mean daily dose 1,849 mg/day (SD 536)<br><br>Duration of treatment: patients received DR cysteamine bitartrate for 3 weeks and then crossed over to IR cysteamine bitartrate for 3 weeks, or vice versa<br><br>Patients continued with all concomitant treatments. PPI use was permitted during IR cysteamine bitartrate treatment but was intended to be discontinued during treatment with DR cysteamine bitartrate[b] | Crossover trial: 3 weeks for each treatment period<br><br>**Critical outcomes**<br>• Disease response<br>• WBC cystine levels (nmol hemicystine/mg protein)<br><br>**Important outcomes**<br>• Safety<br>• Total number of AEs<br>• Total number of SAEs |
| Langman et al 2014<br>Prospective single-arm follow-up to crossover RCT (Langman et al 2012)<br>Multicentre (3 centres in the USA and 5 in France and the Netherlands) | n=40 patients with confirmed nephropathic cystinosis<br><br>DR cysteamine bitartrate: n=40<br><br>Male: 23 (57.5%)<br><br>Age (years)<br>All patients, mean (SD): 11.5 (3.6)<br>Children (aged between 6 and ≤12 years), n: 25<br>Adolescents (aged between 12 and ≤21 years), n: 15 | **Intervention**<br>DR cysteamine bitartrate every 12 hours: total daily dose (mean % of previous IR cysteamine dose) 83.7 (SD 7.9):<br><br>**Comparison**<br>None<br><br>Growth hormones were permitted, but no further details were reported<br><br>Duration of treatment: 24 months | Follow-up: 24 months (long-term follow-up to Langman et al 2012)<br><br>**Critical outcomes**<br>• Disease response<br>• WBC cystine levels (nmol hemicystine/mg protein)<br>• Progression of cystinosis associated renal disease<br>• eGFR (mL/min/1.73m$^2$)<br>• Need for renal transplant<br>• Need for renal dialysis<br><br>**Important outcomes**<br>• Quality of life |

| Study | Population | Intervention and comparison | Outcomes reported |
|---|---|---|---|
| | No relevant subgroups reported | | • % change in PedsQL[c]<br>• Growth measurements<br>  • Z-score (height)[d]<br>  • BMI (kg/m$^2$)<br>• Safety<br>  • Number of patients experiencing at least 1 treatment-related AE |
| Vaisbich et al 2022<br>Prospective case series<br>Brazil and the USA | n=15 children with confirmed nephropathic cystinosis<br><br>DR cysteamine: n=15<br><br>Male: 8 (53.3%)<br>Age (years), mean (SD; range): 2.2 (1.0; 1.0 to 4.5)<br>Ethnicity (white), n (%): 11 (73.3)<br><br>No relevant subgroups reported | **Intervention**<br>DR cysteamine bitartrate every 12 hours: recommended target dose 1 g/m$^2$/day<br>Final dose (n=14): 200 to 600 mg per day<br><br>**Comparison**<br>None<br><br>All patients (100%) reported using at least one concomitant treatment, which was started or continued after the first dose of study drug<br><br>Duration of treatment: 0.5 months [1 patient received only 1 dose of DR cysteamine] to 21 months | Follow-up: at interim timepoints up to 18 months and/or study exit (timeframe not clear)[e]<br><br>**Critical outcomes**<br>• Disease response<br>  • WBC cystine levels in mg ½ cystine/mg protein)<br>  • Proportion of patients who reached WBC cystine levels <1 nmol hemicystine/mg protein)<br>• Progression of cystinosis associated renal disease<br>  • eGFR (ml/min/1.73m$^2$)<br><br>**Important outcomes**<br>• Growth measurements[f]<br>  • Z-score (height)<br>  • Z-score (weight)<br>  • Z-score (BSA)<br>  • Z-score (BMI)<br>• Safety<br>  • Number of patients with any AE<br>  • Number of patients with SAEs |

**Abbreviations**

AE: adverse event; BMI: body mass index; BSA: body surface area; DR: delayed-release; eGFR: estimated glomerular filtration rate; IR: immediate-release; kg: kilogram; m: metre; mg: milligram; ml: millilitre; min: minute; nmol: nanomole; PedsQL: paediatric quality of life inventory; PPI: proton pump inhibitor; RCT: randomised controlled trial; SA: short-acting; SAE: serious adverse event; SD: standard deviation; USA: United States of America; VAS: visual analogue scale; WBC: white blood cell.

**Footnotes**

a. Patients evaluated their adherence answering the following question on a visual analogical scale: *"How do you evaluate your adherence to cysteamine?"* at each study visit; no further details were provided, but we have assumed this was measured using a score of 1 to 10. Individual average of self-reported adherence over the year.

b. PPI use during treatment with DR mercaptamine bitartrate was intended to be discontinued to maintain an optimal pH level in the stomach for optimal kinetics of the intervention.

| Study | Population | Intervention and comparison | Outcomes reported |
|---|---|---|---|
| c. PedsQL is a paediatric quality of life questionnaire assessing four areas of functionality: physical, emotional, social, and school. Details on the PedsQL scoring algorithm were not reported, but higher values indicate better health related quality of life.<br>d. Height Z-score for age was calculated using the Centres of Diseases Control and Prevention growth charts.<br>e. Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.<br>f. Z-scores were based on the Centre for Disease Control and Prevention growth data for the general population. | | | |

# 5. Results

## In people with nephropathic cystinosis what is the clinical effectiveness and safety of delayed-release mercaptamine bitartrate compared to current standard care?[12]

| Outcome | Evidence statement |
|---|---|
| **Clinical Effectiveness** | |
| **Critical outcomes** | |
| **Disease response**<br>**Certainty of evidence:**<br>Very low to low | This outcome is important to patients because it reflects how effective the treatment is at preventing disease progression.<br>One three week crossover RCT, one prospective single-arm study [long-term follow-up to the crossover RCT], one prospective cohort study, and one prospective case series provided evidence relating to disease response in patients with nephropathic cystinosis. Disease response was defined as WBC/leukocyte cystine levels (nmol hemicystine/mg protein) in all four papers. The single-arm follow-up study, cohort study, and case series also provided evidence on the proportion of patients or study visits where WBC/leukocyte cystine levels were <1nmol hemicystine/mg protein[13] during treatment with DR mercaptamine bitartrate. The follow-up durations ranged from three weeks to 24 months.<br>WBC/leukocyte cystine levels (nmol hemicystine/mg protein)<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>**At three week crossover**<br>• One three week crossover RCT (Langman et al 2012; n=41) showed that mean WBC cystine levels remained optimal (i.e. ≤1 nmol hemicystine/mg protein) in patients with nephropathic cystinosis when treated with DR cysteamine bitartrate and IR cysteamine bitartrate (LSM [SEM]: 0.70 [0.19] and 0.97 [0.19] nmol hemicystine/mg protein, respectively), although three patients treated with IR cysteamine bitartrate had a mean WBC cystine level >2 nmol hemicystine/mg protein and were considered *"not well controlled"*. The difference between treatment groups was *statistically significant* (LSM [SEM; 95.8% CI]:[14] -0.27 nmol hemicystine/mg protein [0.36; -0.63 to 0.09]; p<0.001) and indicated greater benefit with DR cysteamine bitartrate[15]. **(LOW)**<br>*DR mercaptamine bitartrate vs no comparator*<br>**At 12 months follow-up**<br>• One prospective cohort study (Gaillard et al 2021; n=17) showed an increase in leukocyte cystine levels from baseline to 12 months follow-up during treatment with DR cysteamine bitartrate in patients with nephropathic cystinosis (median: 0.3 nmol hemicystine/mg protein [range 0.1 to 2.5] to 1.1 nmol hemicystine/mg protein [range 0.3 to 2.7], respectively), with the median follow-up result being greater than the optimal target of ≤1 nmol hemicystine/mg protein. No statistical measures were reported. **(VERY LOW)** |

[12] Mercaptamine bitartrate is described differently in the included papers. For the purposes of this review, the terms referred to in the individual papers are used when referring to an individual paper (i.e. delayed release [DR] cysteamine/cysteamine bitartrate [RP103 or Procysbi] or immediate-release [IR] or short-acting [SA] cysteamine/cysteamine bitartrate [Cystagon]), and DR or IR mercaptamine bitartrate are used when summarising the results for an outcome.
[13] The PICO document states that the target white cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.
[14] The authors stated that they used the 95.8% CI instead of 95% CI to take into account a sample size re-estimation calculation that was performed after 20 patients were enrolled.
[15] The upper end of the confidence interval (0.09) was lower than the 0.3 nmol hemicystine/mg protein noninferiority limit that the authors defined *a priori*.

| Outcome | Evidence statement |
|---|---|
| | **At study exit (timeframe not clear)**[16]<br>• One prospective case series (Vaisbich et al 2022; n=13) reported that DR cysteamine bitartrate resulted in a *"clinically meaningful*" decrease (i.e. improvement) in WBC cystine levels from baseline to study exit in children with nephropathic cystinosis (mean: 3.2 nmol hemicystine/mg protein [SD 3.0] to 0.8 nmol hemicystine/mg protein [SD 0.8], respectively). The definition of a clinically meaningful effect size was not reported, but the change from baseline was *statistically significant* (p=0.04). **(VERY LOW)**<br><br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that WBC cystine levels *"were maintained under optimal control (<1 nmol hemicystine/mg protein)"* from baseline to 24 months follow-up during treatment with DR cysteamine bitartrate (mean: 0.43 nmol hemicystine/mg protein [SD 0.15] to 0.55 nmol hemicystine/mg protein [SD 0.34], respectively) in patients with nephropathic cystinosis. The change from baseline was *not statistically significant* (p=0.38). **(VERY LOW)**<br><br><u>Proportion of visits or participants with WBC/leukocyte cystine levels ≤1 nmol hemicystine/mg protein</u><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence was identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At 12 months follow-up**<br>• One prospective cohort study (Gaillard et al 2021; n=17) reported that for each patient with nephropathic cystinosis, the median proportion of visits with leukocyte cystine levels ≤1 nmol hemicystine/mg protein[17] was 60% (range 0% to 100%) during 12 months follow-up with DR cysteamine treatment. No statistical measures were reported. **(VERY LOW)**<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=13) reported that the proportion of children with nephropathic cystinosis who reached optimal WBC cystine levels (i.e. <1.0 nmol hemicystine/mg protein) increased from 20.0% (three of 15 children) at baseline to 76.9% (10 of 13 children) at study exit. No statistical measures were reported. **(VERY LOW)**<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that *"mean WBC (cystine) remained below 1 nmol ½ cystine/mg protein during the entire study"*[18] in patients with nephropathic cystinosis who were treated with DR cysteamine bitartrate. No further details were reported. **(VERY LOW)**<br><br>**DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**One three week crossover RCT provided low certainty evidence that mean WBC cystine levels remained optimal (i.e. ≤1 nmol hemicystine/mg protein) in** |

[16] Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.
[17] Defined as individual percentage of visits with leukocyte cystine levels ≤ 1 nmol hemicystine/mg protein.
[18] ½ cystine/mg protein also referred to as hemicystine/mg protein.

| Outcome | Evidence statement |
|---|---|
| | **patients when they were treated with DR cysteamine bitartrate and when they were treated with IR cysteamine bitartrate, but there was a *statistically significant* difference between treatment groups which indicated greater benefit with DR cysteamine bitartrate.**<br>**DR mercaptamine bitartrate vs no comparator:**<br>**One prospective single-arm follow-up study, one prospective cohort study, and one prospective case series provided very low certainty evidence showing mixed findings. One prospective cohort study showed that WBC/leukocyte cystine levels increased from baseline to 12 months follow-up, with the median follow-up results being greater than the optimal target of ≤1 nmol hemicystine/mg protein, but no statistical measures were reported. One prospective case series reported a *"clinically meaningful"* decrease (i.e. improvement) in WBC cystine levels from baseline to study exit (timeframe not clear and the definition of a clinically meaningful effect size was not provided), and one prospective single-arm follow-up study reported that WBC cystine levels *"were maintained under optimal control (<1 nmol hemicystine/mg protein)"* from baseline to 24 months follow-up. These three studies also reported that WBC/leukocyte cystine levels were optimal (i.e. ≤1 nmol hemicystine/mg protein) at follow-up for a median of 60% of visits for each patient, or for 76.9% or 100% of patients, respectively.** |
| **Treatment adherence**<br>**Certainty of evidence:**<br>Very low | Treatment adherence is important to patients as it provides an indication of how well the treatment is tolerated. Effective treatment of nephropathic cystinosis requires good compliance to reduce cystine-crystal accumulation in cells. Good adherence can postpone time to developing renal failure requiring dialysis or transplant.<br>One prospective cohort study provided comparative and non-comparative evidence on treatment adherence in patients with nephropathic cystinosis. Two different scores were used to measure adherence at 12 months follow-up; objective measures (i.e. electronic caps) were used to compare adherence to treatment with DR cysteamine versus SA cysteamine, while subjective measures (i.e. self-reported) were used to assess adherence to DR cysteamine for all patients (i.e. including the four patients who initially received SA cysteamine).<br>Adherence score[19] [0 to 2[20]], measured using electronic caps (MEMs®)[21]<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>**At 12 months follow-up**<br>• One prospective cohort study (Gaillard et al 2021; n=17) reported higher adherence scores at 12 months follow-up when patients with nephropathic cystinosis were treated with DR cysteamine (median score: 1.8 [range 0.1 to 2.0; n=17, including the four patients initially receiving SA cysteamine)[22] compared to initial treatment with SA cysteamine (median score: 0.5 [range 0.3 to 1.0]; n=4). No statistical measures were reported. **(VERY LOW)**<br>*DR mercaptamine bitartrate vs no comparator*<br>No evidence was identified for this outcome. |

[19] Individual average of daily adherence scores.
[20] Good adherence (score 2); partial adherence (score 1); poor adherence (score 0). Scores were defined according to the number of intakes per 24 hours and the length of delay between intake and the theoretical action time for each formulation of cysteamine (i.e. 12 or 6 hours)
[21] Electronic caps (MEMs®) were adapted to existing bottles of cysteamine. Electronic monitoring is a method for compiling drug dosing histories, integrating a small microcircuit into drug packages and recording the time and date (i.e. opening) whenever it detects that a dose of drug is removed from the bottle.
[22] Among the 17 enrolled patients, four patients received SA cysteamine at inclusion, for 26, 26, 29, and 91 days respectively. Then, they were switched to DR cysteamine for 366, 381, 336, and 283 days, respectively.

| Outcome | Evidence statement |
|---|---|
| | **Adherence level,[23] measured using electronic caps (MEMs®)**<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>**At 12 months follow-up**<br>• One prospective cohort study (Gaillard et al 2021; n=17) reported that at 12 months follow-up, a greater proportion of patients with nephropathic cystinosis had a good adherence score (of 2) when treated with DR cysteamine (median: 88% [range 1% to 99%]; n=17, including the four patients initially receiving SA cysteamine) compared to initial treatment with SA cysteamine (median: 2% [range 0% to 22%]; n=4). No statistical measures were reported. **(VERY LOW)**<br>• One prospective cohort study (Gaillard et al 2021; n=17) reported that at 12 months follow-up, a greater proportion of patients with nephropathic cystinosis had a partial or good adherence score (of 1 or 2) when treated with DR cysteamine (median: 91% [range 5% to 99%]; n=17, including the four patients initially receiving SA cysteamine) compared to initial treatment with SA cysteamine (median: 43% [range 27% to 78%]; n=4). The authors reported that three of four patients initially receiving SA cysteamine reported higher partial or good adherence scores when receiving DR cysteamine (74%, 75% and 92%) compared to SA cysteamine (27%, 52% and 78%). The fourth patient had similar adherence scores during DR and SA cysteamine treatment (40% and 35%, respectively). No statistical measures were reported. **(VERY LOW)**<br>*DR mercaptamine bitartrate vs no comparator*<br>No evidence was identified for this outcome.<br>Self-reported adherence [VAS score][24]<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence was identified for this outcome.<br>*DR mercaptamine vs no comparator*<br>**At 12 months follow-up**<br>• One prospective cohort study (Gaillard et al 2021; n=17) reported high levels of self-reported adherence at 12 months follow-up in patients with nephropathic cystinosis (median score: 9 [range 4 to 10]). **(VERY LOW)**<br>**DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**One prospective cohort study provided very low certainty evidence showing greater adherence to treatment (scored using objective measures) at 12 months follow-up when patients were treated with DR cysteamine compared to initial treatment with SA cysteamine, but no statistical measures were reported.**<br>**DR mercaptamine bitartrate vs no comparator:**<br>**One prospective cohort study provided very low certainty evidence showing high self-reported adherence (scored using subjective measures) at 12 months in patients with nephropathic cystinosis treated with DR cysteamine treatment.** |
| **Progression of cystinosis associated renal disease**<br>**Certainty of evidence:** | This outcome is important, as a goal of effective treatment would be to postpone the physical health consequences of cystinosis such as renal failure requiring dialysis or transplant which would have negative mental and physical health consequences to patients. |

[23] Individual percentage of days at the corresponding score level.
[24] Individual average of self-reported adherence over the year. Participants evaluated their adherence answering the following question on a visual analogical scale: *"How do you evaluate your adherence to cysteamine?"* at each study visit; no further details were provided, but we have assumed this was measured using a score of 1 to 10.

| Outcome | Evidence statement |
|---|---|
| Very low | One prospective single-arm study [long-term follow-up to the crossover RCT], one prospective cohort study, and one prospective case series provided non-comparative evidence relating to progression of cystinosis associated renal disease in patients with nephropathic cystinosis. These three studies provided evidence on eGFR during treatment with DR mercaptamine bitartrate from two weeks to 24 months follow-up. The prospective single-arm follow-up study also reported the number of patients needing renal transplant or renal dialysis at 24 months follow-up.<br><br>eGFR (ml/min/1.73m$^2$)<br><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br><br>No evidence identified for this outcome.<br><br>*DR mercaptamine bitartrate vs no comparator*<br><br>**At two weeks follow-up**<br><br>• One prospective case series (Vaisbich et al 2022; n=NR[25]) showed an increase (i.e. improvement) in eGFR from baseline to two weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 57.62 ml/min/1.73m$^2$ [SD 19.35], respectively). No statistical measures were reported. **(VERY LOW)**<br><br>**At six weeks follow-up**<br><br>• One prospective case series (Vaisbich et al 2022; n=NR) showed that eGFR was similar at baseline and six weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 55.43 ml/min/1.73m$^2$ [SD 17.41], respectively). No statistical measures were reported. **(VERY LOW)**<br><br>**At 10 weeks follow-up**<br><br>• One prospective case series (Vaisbich et al 2022; n=NR) showed a decrease (i.e. decline) in eGFR from baseline compared to 10 weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 53.83 ml/min/1.73m$^2$ [SD 17.72], respectively). No statistical measures were reported. **(VERY LOW)**<br><br>**At six months follow-up**<br><br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to six months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 61.27 ml/min/1.73m$^2$ [SD 15.47], respectively). No statistical measures were reported. **(VERY LOW)**<br><br>**At nine months follow-up**<br><br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to nine months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 61.71 ml/min/1.73m$^2$ [SD 23.43], respectively). No statistical measures were reported. **(VERY LOW)**<br><br>**At 12 months follow-up**<br><br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to 12 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 60.92 ml/min/1.73m$^2$ [SD 25.63], respectively). No statistical measures were reported. **(VERY LOW)** |

[25] The paper included 15 patients at baseline and 14 patients at 'study exit', but the number of patients assessed at other timepoints was not reported and could not be determined from the graphical presentation.

| Outcome | Evidence statement |
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| | • One prospective cohort study (Gaillard et al 2021; n=15) reported that the median eGFR at baseline was 61.5 ml/min/1.73m$^2$ (range 7.9 to 132.2) in patients with nephropathic cystinosis and that *"GFR remained stable over the year in our cohort of patients"*. No further details were reported and no statistical measures were presented. **(VERY LOW)**<br>**At 18 months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase (i.e. improvement) in eGFR from baseline compared to 18 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 67.20 ml/min/1.73m$^2$ [SD 31.17], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=14) showed an increase in eGFR from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: 55.93 ml/min/1.73m$^2$ [SD 22.43] to 63.79 ml/min/1.73m$^2$ [SD 21.44], respectively). The mean change from baseline to study exit was 8.14 ml/min/1.73m$^2$ (SD 15.48), but no statistical measures were reported. **(VERY LOW)**<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was *no statistically significant* difference in eGFR from baseline to 24 months follow-up in patients with nephropathic cystinosis (mean: 63 ml/min/1.73m$^2$ [SD 25] to 57 ml/min/1.73m$^2$ [SD 25], respectively; p=0.32). **(VERY LOW)**<br><br><u>Number of patients needing renal transplant</u><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence was identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT; n=40) reported that one patient treated with DR cysteamine bitartrate for nephropathic cystinosis underwent renal transplant at 17 months. **(VERY LOW)**<br><u>Number of patients needing renal dialysis</u><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence was identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that one patient treated with DR cysteamine bitartrate for nephropathic cystinosis withdrew from the study at 21 months due to a decline in eGFR and need for renal dialysis. **(VERY LOW)**<br>**DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**No evidence was identified for progression of cystinosis associated renal disease.**<br>**DR mercaptamine bitartrate vs no comparator:**<br>**One prospective single-arm follow-up study, one prospective cohort study, and one prospective case series provided very low certainty evidence** |

| Outcome | Evidence statement |
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| | **relating to progression of cystinosis associated renal disease in patients with nephropathic cystinosis treated with DR mercaptamine bitartrate. One prospective cohort study reported that *"GFR remained stable over the year in our cohort of patients",* but no further details were reported. One prospective case series reported an increase (i.e. improvement) in eGFR from baseline up to study exit (timeframe not clear), but no statistical measures were reported. The prospective single-arm follow-up study reported that there were *no statistically significant* differences in eGFR from baseline to 24 months follow-up, although one patient each underwent renal transplant or renal dialysis.** |
| **Important outcomes** | |
| **Quality of life**<br>**Certainty of evidence:**<br>Very low | Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making.<br>One prospective single-arm study [long-term follow-up to the crossover RCT] provided evidence on quality of life in patients with nephropathic cystinosis up to 24 months follow-up, measured using the PedsQL[26].<br>Percentage change in PedsQL - intercept[27]<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>**Unclear follow-up [from three week crossover RCT to enrolment in the follow-up study)**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was a *statistically significant* improvement in two of four PedsQL subscale scores and the total score in patients with nephropathic cystinosis when comparing scores assessed during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine in the single-arm follow-up study: social function (p=0.049), school function (p=0.004), and total function (p=0.048), but there was *no statistically significant* difference in the subscale scores for physical function (p=0.160) and emotional function (p=0.136). **(VERY LOW)**<br>*DR mercaptamine bitartrate vs no comparator*<br>No evidence identified for this outcome.<br>Percentage change in PedsQL - slope[28]<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there were *no statistically significant* differences in any PedsQL subscale score or total score from baseline to 24 months follow-up in patients with nephropathic cystinosis treated with DR cysteamine: physical function (p=0.054), emotional function (p=0.890), social |

[26] PedsQL is a paediatric quality of life questionnaire assessing four areas of functionality: physical, emotional, social, and school. Details on the PedsQL scoring algorithm were not reported, but higher values indicate better health related quality of life.
[27] The intercept value (LSM) represents the change from the value during treatment with IR cysteamine from the prior three week crossover RCT (Langman et al 2012).
[28] The slope represents the change from baseline to 24 months during treatment with DR cysteamine in the single-arm follow-up study to the crossover RCT.

| Outcome | Evidence statement |
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| | function (p=0.201), school function (p=0.126), and total function (p=0.072). **(VERY LOW)**<br>**DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**One prospective single-arm follow-up study provided very low certainty evidence that there was a *statistically significant* improvement in two of four paediatric quality of life subscale scores and the total score in patients with nephropathic cystinosis when comparing scores during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine during the single-arm follow-up study.**<br>**DR mercaptamine bitartrate vs no comparator:**<br>**One prospective single arm follow-up study provided very low certainty evidence that when patients were treated with DR cysteamine there was *no statistically significant* change in any of the paediatric quality of life subscale scores or total score from the follow-up study baseline to 24 months follow-up.** |
| **Growth measurements**<br>**Certainty of evidence:**<br>Very low | Growth measurements such as weight and height are important outcomes to patients and their carers as they can be a marker of treatment success. This is particularly valued by the paediatric patient cohort.<br>One prospective single-arm study [long-term follow-up to the crossover RCT], and one prospective case series provided evidence on growth measures in patients with nephropathic cystinosis. Growth measurements included height, weight, BSA, and BMI, mainly measured using Z-scores, and results were reported at two weeks to 24 months follow-up.<br>Z-score (height)[29]<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At two weeks follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline to two weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [ SD 1.6] to -2.9 [SD 1.5], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At 12 weeks follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline to 12 weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -2.5 [SD 1.5], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At six months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline compared to six months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -2.0 [SD 1.7], respectively). No statistical measures were reported. **(VERY LOW)** |

[29] Z-scores were based on the Centre for Disease Control and Prevention (CDC) growth data for the general population.

| Outcome | Evidence statement |
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| | **At 12 months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline compared to 12 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to -1.1 [SD 1.9], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At 18 months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in height Z-score from baseline compared to 18 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to 0.1 [SD 2.1], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=15) showed an increase in height Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -3.2 [SD 1.6] to 0.1 [SD 2.0], respectively). The authors stated that the increase was "*clinically meaningful"*, but the definition of a clinically meaningful effect size was not provided and no statistical measures were reported. **(VERY LOW)**<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was *no statistically significant* difference in height Z-score in patients with nephropathic cystinosis from baseline (mean: −1.15 [SD −0.93]) to 24 months follow-up (mean: -1.21 [SD -0.96]; p=0.46). **(VERY LOW)**<br>Z-score (weight)[29]<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At two weeks follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline to two weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -3.9 [SD 2.1], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At 12 weeks follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline to 12 weeks follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -3.3 [SD 2.1], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At six months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline compared to six months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -2.8 [SD 2.3], respectively). No statistical measures were reported. **(VERY LOW)** |

| Outcome | Evidence statement |
|---|---|
| | **At 12 months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline compared to 12 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -2.2 [SD 1.7], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At 18 months follow-up**<br>• One prospective case series (Vaisbich et al 2022; n=NR) showed an increase in weight Z-score from baseline compared to 18 months follow-up in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -1.3 [SD 2.0], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=15) showed an increase in weight Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -4.0 [SD 2.1] to -1.1 [SD 1.8], respectively). The authors stated that the increase was *"clinically meaningful"*, but the definition of a clinically meaningful effect size was not provided and no statistical measures were reported. **(VERY LOW)**<br><u>BMI</u><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=14) showed a slight decrease in BMI Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -1.0 [SD 1.1] to -1.2 [SD 1.3], respectively). No statistical measures were reported. **(VERY LOW)**<br>**At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that there was *no statistically significant* difference in BMI in patients with nephropathic cystinosis from baseline (mean: 18.2 kg/m$^2$ [SD 3.1]) to 24 months follow-up (mean: 18.3 kg/m$^2$ [SD 3.2]; p=0.27). **(VERY LOW)**<br><u>Z-score (BSA)[29]</u><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>No evidence identified for this outcome.<br>*DR mercaptamine bitartrate vs no comparator*<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=14) showed an increase in BSA Z-score from baseline compared to study exit in children with nephropathic cystinosis treated with DR cysteamine bitartrate (mean: -1.8 [SD 1.1] to -1.3 [SD 1.1], respectively). The authors stated that the increase was *"clinically meaningful"*, but the definition of a clinically meaningful effect size was not provided and no statistical measures were reported. **(VERY LOW)**<br>**DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**No evidence was identified on growth measurements.** |

| Outcome | Evidence statement |
|---|---|
| | **DR mercaptamine bitartrate vs no comparator:**<br>**One prospective single-arm follow-up study and one prospective case series provided very low certainty evidence relating to growth measurements in patients with nephropathic cystinosis treated with DR cysteamine bitartrate. One prospective case series reported a *"clinically meaningful"* increase (i.e. improvement) in height, weight and BSA Z-scores from baseline to study exit (timeframe not clear and the definition of a clinically meaningful effect size was not provided), but no statistical measures were reported. One prospective single-arm study reported that there were *no statistically significant* differences from baseline to 24 months follow-up in BMI or height Z-score.** |
| **Activities of daily living**<br>**Certainty of evidence:**<br>Not applicable | ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.<br>No evidence was identified for this outcome. |
| **Progression of non-renal cystinosis associated disease**<br>**Certainty of evidence:**<br>Not applicable | This outcome is important, as a goal of effective treatment would be to postpone the physical health consequences of cystinosis such as diabetes, hypothyroidism, muscle wasting and central nervous system involvement. To postpone or reduce the development of these complications would be valuable to patients as it would indicate an improvement in their overall health.<br>No evidence was identified for this outcome. |
| **Safety** | |
| **Frequency of adverse events**<br>**Certainty of evidence:**<br>Very low to low | These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.<br>One crossover RCT, one prospective single-arm study [long-term follow-up to the crossover RCT], one prospective case series provided evidence on the occurrence of AEs in patients with nephropathic cystinosis. The follow-up durations ranged from three weeks to 24 months.<br><u>Total number of AEs</u><br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>**At three week crossover**<br>• One three week crossover RCT (Langman et al 2012; n=41) reported a greater number of AEs during treatment with DR cysteamine bitartrate compared to IR cysteamine bitartrate in patients with nephropathic cystinosis (69 versus 25 AEs, respectively). The most common AEs were gastrointestinal disorders (n=31 in the DR cysteamine bitartrate group [23 were considered treatment-related and eight not treatment-related], n=11 in the IR cysteamine bitartrate group [eight were considered treatment-related and three not treatment-related]). No statistical measures were reported. **(LOW)**<br>*DR mercaptamine bitartrate vs no comparator*<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=15) reported that all children (100%) with nephropathic cystinosis experienced an AE during treatment with DR cysteamine bitartrate, but it was unclear whether they were treatment-related. **(VERY LOW)** |

| Outcome | Evidence statement |
|---|---|
| | **At 24 months follow-up**<br>• One prospective single-arm study (Langman et al 2014 [follow-up to three week crossover RCT]; n=40) reported that all 40 (100%) patients with nephropathic cystinosis experienced a treatment-related AE up to 24 months follow-up. The most commonly occurring AE was gastrointestinal disorders which were experienced by 35 (87.5%) patients. **(VERY LOW)**<br>**DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**One three week crossover RCT provided low certainty evidence showing a greater number of AEs occurred when patients were treated with DR cysteamine bitartrate compared to when they were treated with IR cysteamine bitartrate. For the most common AE (gastrointestinal disorders), most were considered to be treatment-related in both treatment arms. No statistical measures were reported.**<br>**DR mercaptamine bitartrate vs no comparator:**<br>**One prospective single-arm follow-up study and one prospective case series provided very low certainty evidence that all patients experienced an AE during treatment with DR cysteamine bitartrate; it was unclear whether the AEs were treatment-related in the case series, but all AEs were treatment-related in the single-arm follow-up study.** |
| **Frequency of grade 3 or 4 adverse events**<br>**Certainty of evidence:**<br>Very low to low | These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.<br>One crossover RCT and one prospective case series provided evidence on the occurrence of SAEs (grade ≥3) in patients with nephropathic cystinosis. The follow-up durations ranged from three weeks to at least 18 months.<br>Total number of SAEs<br>*DR mercaptamine bitartrate vs IR mercaptamine bitartrate*<br>**At three week crossover**<br>• One three week crossover RCT (Langman et al 2012; n=41) reported a greater number of SAEs during treatment with DR cysteamine bitartrate compared to IR cysteamine bitartrate in patients with nephropathic cystinosis (six versus one, respectively). For DR cysteamine bitartrate, three SAEs were gastrointestinal disorders, with one considered treatment-related and two not treatment-related. One SAE was related to metabolic and nutrition disorders, but not considered to be treatment-related. The remaining two SAEs were injury or procedural related and not treatment-related. For IR cysteamine bitartrate, the one SAE (vascular disorder) was not considered treatment-related. No statistical measures were reported. **(LOW)**<br>*DR mercaptamine bitartrate vs no comparator*<br>**At study exit (timeframe not clear)**<br>• One prospective case series (Vaisbich et al 2022; n=15) reported that DR cysteamine bitartrate resulted in a total of 36 SAEs which occurred in 12 (80.0%) patients with nephropathic cystinosis at study exit. This included five patients with gastroenteritis, four patients each with dehydration or vomiting, two patients each with electrolyte imbalance or gastrostomy, and one patient with other SAEs who was hospitalised and died the next day.[30] None of the SAEs were considered to be treatment-related. **(VERY LOW)** |

[30] This patient had four grade five AEs: gastroenteritis, cardiopulmonary failure, Fanconi syndrome, and hypovolemic shock.

| Outcome | Evidence statement |
|---|---|
| | **DR mercaptamine bitartrate vs IR mercaptamine bitartrate:**<br>**One three week crossover RCT provided low certainty evidence showing a greater number of SAEs when patients were treated with DR cysteamine bitartrate compared to when they were treated with IR cysteamine bitartrate, with most not considered treatment-related. No statistical measures were reported.**<br>**DR mercaptamine bitartrate vs no comparator:**<br>**One prospective case series provided very low certainty evidence that the majority of patients experienced at least one SAE, including one patient who died, but none were considered to be treatment-related.** |
| **Abbreviations**<br>ADLs: activities of daily living; AE: adverse event; BMI: body mass index; BSA: body surface area; CI: confidence interval; DR: delayed-release; eGFR: estimated glomerular filtration rate; IR: immediate-release; LSM: least squares mean; MEMs: medication event monitoring system; m: metre; mg: milligram; min: minute; ml: millilitre; N: number; NR: not reported; nmol: nanomole; PedsQL: paediatric quality of life inventory; RCT: randomised controlled trial; SA: short-acting; SAE: serious adverse event; SD: standard deviation; SEM: standard error of the mean; VAS: visual analogue scale; WBC: white blood cell. | |

## In people with nephropathic cystinosis, what is the cost effectiveness of delayed-release mercaptamine bitartrate compared to current standard care?

| Outcome | Evidence statement |
|---|---|
| **Cost effectiveness** | No evidence was identified for cost effectiveness. |

## From the evidence selected, are there any subgroups of patients that may benefit from delayed-release mercaptamine bitartrate more than the wider population of interest?

| Subgroup | Evidence statement |
|---|---|
| **Patients with nephropathic cystinosis aged ≤11 years vs aged >11 years** | One prospective cohort study (Gaillard et al 2021) reported subgroup results in patients with nephropathic cystinosis by age group ≤11 years versus >11 years for the critical outcome treatment adherence, defined as percentage of days with good adherence.[31] Adherence scores were during treatment with DR or SA cysteamine.<br>**Critical outcomes**<br><br>**Treatment adherence**<br>One prospective cohort study (Gaillard et al 2021; n=17) reported that patients with nephropathic cystinosis aged ≤11 years experienced a greater percentage of days with a good adherence score (whether receiving DR or SA cysteamine) compared to patients aged >11 years (median [range]: 89% [80% to 99%] and 68% [1% to 99%], respectively); statistical measures were not reported.<br>**One prospective cohort study reported that patients with nephropathic cystinosis aged ≤11 years experienced a greater percentage of days with a good adherence score compared to patients aged >11 years (whether receiving DR or SA cysteamine), but statistical measures were not reported.** |

[31] Adherence to treatment was assessed using objective measures (i.e. electronic caps [MEMs®]).

**Abbreviations**

DR: delayed-release; N: number; SA: short-acting.

# 6. Discussion

This review examined the clinical effectiveness, safety and cost effectiveness of delayed-release (DR) mercaptamine bitartrate compared to current standard care in people of all ages with nephropathic cystinosis. The critical outcomes of interest were disease response, treatment adherence, and progression of cystinosis associated renal disease. The important outcomes of interest were quality of life (QoL), growth measurements, activities of daily living (ADLs), progression of non-renal cystinosis associated disease, and safety.

Evidence for the clinical effectiveness of DR mercaptamine bitartrate and safety was available from four papers. One paper was a three week crossover RCT (Langman et al 2012) that provided evidence on the effectiveness and safety of DR cysteamine bitartrate compared to immediate-release (IR) cysteamine bitartrate in patients with nephropathic cystinosis. One paper (Langman et al 2014) was a prospective single-arm follow-up study to the crossover RCT (Langman et al 2012) which provided evidence up to two years in patients with nephropathic cystinosis treated with DR cysteamine bitartrate. One paper was a prospective cohort study (Gaillard et al 2021). that included patients with nephropathic cystinosis who were treated with DR cysteamine or short-acting (SA) cysteamine. Four of the included patients initially received SA cysteamine at study inclusion but then switched to DR cysteamine for most of the study duration. The other 13 patients received DR cysteamine throughout the whole study duration. One paper was a prospective case series (Vaisbich et al 2022) that provided evidence assessing DR cysteamine bitartrate in children with nephropathic cystinosis. Treatment doses were reported differently across the studies: one paper reported a daily dose ranging from 200 to 600 mg, one paper reported a median dosage per body surface area (BSA) of 1.06 mg/m$^2$/day, one reported a mean percentage of previous IR cysteamine dose of 83.7%.

Sample sizes were small in all of the included studies (ranging from 15 to 43 patients). The studies were all multicentre and conducted in Brazil and the USA (one study); France (one study); France, the Netherlands and the USA (one study, two papers). Baseline characteristics of the included patients differed within and across studies in terms of age and whether patients had their native kidneys, had undergone kidney transplantation, or were receiving kidney dialysis. The crossover RCT and follow-up study (Langman et al 2012 and 2014) included mainly children and adolescents with a mean age less than 12 years. One prospective cohort study (Gaillard et al 2021) included patients with a median age of 13.9 years (range 5.4 to 33 years) and one prospective case series included only children aged less than six years (Vaisbich et al 2022). The crossover RCT (Langman et al 2012) included only patients with their own kidneys who were well controlled on treatment with IR cysteamine, and the follow-up study (Langman et al 2014) included 40 of 41 patients who had completed the crossover RCT and continued treatment with DR cysteamine. The main uncertainty relates to the serious selection bias due to the inclusion of only patients who were well controlled on treatment as the findings may not be generalisable to patients who are not optimally controlled on treatment. One prospective cohort study (Gaillard et al 2021) included patients already receiving cysteamine, but also a proportion of patients (58.8%) who had previously undergone kidney transplant and a proportion of patients (11.8%) who were receiving kidney dialysis at the time of the study. One prospective case series (Vaisbich et al 2022) included only treatment naïve patients. Outcomes were reported after each three week treatment period in the crossover RCT and at two years in the prospective single-arm follow-up study. The prospective cohort study reported outcomes at 12 months and the prospective case series reported outcomes at interim timepoints up to 18 months follow-up and/or study exit (timeframe not clear)[32].

[32] Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.

The included studies provided limited demographic details. Only one study (Vaisbich et al 2022) reported on ethnicity, which showed a mainly white population (73.3%). The three week crossover RCT and single-arm follow-up study reported a higher proportion of males, while the remaining study reported a greater proportion of females.

Where reported, the use of concomitant treatments differed across the studies. The crossover RCT stated that all concomitant medications (not specified) were continued unchanged during both crossover arms of the study, with the exception of proton pump inhibitors (PPIs). Patients were asked, if possible, to discontinue PPIs during treatment with DR cysteamine bitartrate, but five (27.8%) patients continued to use PPIs. One prospective single-arm follow-up study reported that growth hormones were permitted during the study duration, but no further details were reported. One prospective case series reported that all included patients reported using at least one concomitant treatment or procedure (the most frequent being gastrostomy or reinsertion of G-tube) during the study duration.

One crossover RCT (Langman et al 2012) of 43 patients with nephropathic cystinosis did not clearly report randomisation methods, and concealment of treatment allocation was not possible due to the nature of the study (i.e. crossover), which increases the risk of bias. It was unclear whether the study was sufficiently powered as the authors did not state the sample size calculation or whether it was met. Intention-to-treat (ITT) and per protocol (PP) analyses were conducted, but two patients who withdrew from the study were not included in ITT analysis of the primary outcome (white blood cell [WBC] cystine levels), resulting in the analysis not being based on true ITT methods. The effect of this on the findings is likely to be small, but remains unclear.

The crossover RCT showed a statistically significant benefit with DR cysteamine bitartrate compared to IR cysteamine bitartrate on WBC cystine levels, although mean WBC cystine levels were <1 nmol hemicystine/mg protein during both treatment arms, which is considered optimal[33] and may reflect the fact that only well-controlled patients were included in this RCT. The crossover RCT reported a greater number of adverse events (AEs) and serious adverse events (SAEs) during the DR cysteamine bitartrate treatment period; most of the most commonly reported AEs (gastrointestinal disorders) were considered to be treatment-related while most SAEs were considered not to be treatment-related. The number of gastrointestinal disorders AEs was three times greater during treatment with DR cysteamine bitartrate compared to treatment with IR cysteamine bitartrate. Although there was an 87% reduction in PPI use during treatment with DR cysteamine bitartrate compared to treatment with IR cysteamine bitartrate (based on PP analysis), it was unclear whether the reduction in PPI use was associated with the increase in gastrointestinal related AEs, as the trial was not designed to examine this relationship. The short duration of treatment (i.e. three weeks) for each treatment arm should be taken into consideration, and it was unclear whether there was a sufficient washout period between treatments.

The prospective single-arm follow-up study, prospective cohort study, and prospective case series provided evidence on disease response in 15 to 40 adults and children with nephropathic cystinosis treated with DR mercaptamine bitartrate. One prospective cohort study (Gaillard et al 2021) included four patients who received SA cysteamine at study inclusion who then switched to DR cysteamine after 26 to 91 days, but data were only reported separately in these patients for treatment adherence. The prospective single-arm follow-up study, prospective cohort study, and prospective case series showed mixed findings on WBC cystine levels, but the baseline levels should be taken into account as they varied across the studies for the different populations, i.e. treatment naïve children, or patients previously treated with DR and/or IR

[33] The PICO document states that the target which cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.

mercaptamine bitartrate. The prospective single-arm follow-up study reported that WBC cystine levels remained optimal (i.e. <1 nmol hemicystine/mg protein) from baseline to 24 months follow-up in patients treated with DR cysteamine bitartrate. One prospective case series reported a *"clinically meaningful"* improvement in WBC cystine from baseline to study exit (timeframe not clear and the definition of a clinically meaningful effect size was not provided) after treatment with DR cysteamine in treatment naïve children and this was reflected in the increase in the proportion of patients who reached optimal WBC cystine levels. One prospective cohort study in patients who had previously received oral cysteamine reported an increase in leukocyte cystine levels, with 60% of patient visits showing optimal leukocyte cystine levels.

The prospective single-arm follow-up study, prospective cohort study, and prospective case series also provided evidence on progression of cystinosis associated renal disease (measured as estimated glomerular filtration rate [eGFR]) after treatment with DR mercaptamine bitartrate. The findings were mixed, with one study reporting that *"eGFR remained stable"*, one study showing an improvement in eGFR , and one study reporting no statistically significant change in eGFR. Minimum clinically important differences (MCIDs) were not reported for this outcome.

Two studies provided evidence on growth measurements and safety in patients receiving DR mercaptamine bitartrate. One prospective single-arm follow-up study reported that there was no statistically significant difference in BMI or height Z-score from baseline to 24 months follow-up. One prospective case series reported that there was a *"clinically meaningful"* increase in mean Z-scores for height, weight, and BSA, but there was no change in BMI Z-score, but the definition of a clinically meaningful effect size was not provided. The prospective case series did not provide measurements for all outcomes at each bi-monthly visit and it was not always clear how many patients were included in the data analyses. Although the case series reported this outcome in terms of clinical relevance, MCIDs were not reported in the single-arm follow-up study. Both studies reported that all patients experienced at least one AE and one study reported that the majority of patients experienced at least one SAE.

Limited evidence on quality of life was provided by one prospective single-arm follow-up study which showed statistically significant changes in some PedsQL subscale scores when comparing scores during treatment with IR cysteamine in a previous three week crossover RCT, with no statistically significant change during DR cysteamine treatment in the two year follow-up study. Minimum clinically important differences (MCIDs) were not reported for this outcome.

One prospective cohort study provided evidence on treatment compliance (measured objectively using electronic caps) and reported higher levels of adherence to DR cysteamine at 12 months follow-up compared to initial treatment with SA cysteamine in four patients. The authors reported that three of the four patients who initially received SA cysteamine had higher adherence scores during treatment with DR cysteamine compared to initial treatment with SA cysteamine. It was unclear whether there was a sufficient washout period in these patients, but given the small number of patients, the effect on the findings is likely to be small. The authors also conducted subgroup analysis (patients aged 11 years or younger versus patients older than 11 years) which showed that adherence levels declined in adolescents and adults. The authors suggested that this may reflect the involvement of parents to ensure adherence of younger children with nephropathic cystinosis. Although the evidence for these subgroups of patients has been presented in this evidence review, the findings do not indicate whether there are any subgroups of patients that may benefit more from DR mercaptamine bitartrate more than the wider population of interest. Furthermore, these subgroups do not reflect those specified in the PICO document (i.e. adults versus paediatrics). Patients also self-reported their adherence to treatment, which showed good compliance, but these findings should be interpreted with caution due to the subjective nature of the outcome measure, which can result in risk of bias and the potential for under- or over-reporting of adherence.

No studies were identified that reported activities of daily living (ADLs) or progression of non-renal cystinosis associated disease. No cost effectiveness studies were identified.

The evidence provided by the crossover RCT regarding the effect of DR versus IR cysteamine bitartrate on disease response and safety was considered to be low certainty due to very serious risk of bias. The evidence provided by the prospective single-arm follow-up study, prospective cohort study, and prospective case series regarding the effect of DR mercaptamine bitartrate should be considered as very low certainty due to serious or very serious risk of bias and serious or very serious indirectness due to the prospective cohort study including patients who were initially receiving SA cysteamine bitartrate and then switched to DR cysteamine bitartrate for the remainder of the study; and the lack of a comparator for most outcomes in these studies. Further limitations of the prospective single-arm follow-up study, prospective cohort study, and prospective case series include the small sample sizes, and their observational nature which means that there is uncertainty around whether the effects observed may have been due to confounding factors.

# 7. Conclusion

This review included one three week crossover RCT, one prospective single-arm follow-up study to the crossover RCT, one prospective cohort study and one prospective case series. No evidence was available for two important outcomes (ADLs and progression of non-renal cystinosis associated disease) and no evidence was available on cost effectiveness.

The three week crossover RCT found a statistically significant benefit in disease response with DR cysteamine bitartrate compared to IR cysteamine bitartrate in patients with nephropathic cystinosis, but showed a greater number of adverse events (AEs) and serious adverse events (SAEs) during treatment with DR cysteamine bitartrate. The evidence provided by the crossover RCT should be considered as low certainty due to very serious risk of bias resulting from lack of details on methodology. Furthermore, the short duration of treatment (i.e. three weeks) for each treatment arm should be taken into consideration, and it was unclear whether there was a sufficient washout period between treatments.

Comparative evidence was also provided in one single-arm follow-up study and one prospective cohort study. The single-arm follow-up study showed statistically significant improvement in two quality of life subscale scores and the total score in patients with nephropathic cystinosis, when comparing scores during previous treatment with IR cysteamine (in the three week crossover RCT) to treatment with DR cysteamine during the two year single-arm follow-up study. There was no statistically significant difference in any of the quality of life scores from the follow-up study baseline to two years follow-up.

The prospective cohort study showed higher levels of adherence to DR cysteamine treatment at 12 months follow-up compared to initial treatment with SA cysteamine in four patients. The prospective cohort study also reported treatment adherence in subgroups of patients aged 11 years or younger versus patients older than 11 years (whether receiving DR or SA cysteamine), with the findings showing a decline in adherence levels in adolescents and adults (i.e. 11 years and older). Although the evidence on treatment adherence in these subgroups of patients has been presented in this evidence review, the findings do not indicate whether there are any subgroups of patients that may receive greater clinical benefit from DR mercaptamine bitartrate than the wider population of interest. Furthermore, these subgroups do not reflect those specified in the PICO document (i.e. adult versus paediatric population).

The evidence provided by the prospective single-arm follow-up study, prospective cohort study, and prospective case series should be considered as very low certainty due to the lack of a relevant treatment comparison group, small sample sizes (ranging from 15 to 40 patients), and lack of statistical measures for some outcomes. These three studies reported mixed findings on disease response and progression of cystinosis associated renal disease in patients with nephropathic cystinosis treated with DR mercaptamine bitartrate. The mixed results may reflect the difference in study populations (i.e. different renal function at study enrolment) and different treatment durations. Two of these studies also provided mixed findings on growth measurements, and both studies reported that all patients experienced at least one AE during study treatment, with one of these studies also reporting that most patients experienced at least one SAE. Limited findings were reported by one of these studies on quality of life.

# Appendix A PICO document

The review questions for this evidence review are:

1. In people with nephropathic cystinosis what is the clinical effectiveness of delayed-release mercaptamine bitartrate compared to current standard care?
2. In people with nephropathic cystinosis what is the safety of delayed-release mercaptamine bitartrate compared to current standard care?
3. In people with nephropathic cystinosis what is the cost effectiveness of delayed-release mercaptamine bitartrate compared to current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit more from delayed-release mercaptamine bitartrate more than the wider population of interest?

| | |
|---|---|
| **P – Population and Indication** | People of all ages with confirmed nephropathic cystinosis<br><br>[Diagnosis usually confirmed by elevated white blood cell cystine levels and/or molecular testing of the CTNS gene.]<br><br>Subgroups of interest:<br>• Adult vs paediatric population |
| **I – Intervention** | Delayed-release mercaptamine bitartrate<br><br>[This is an oral medication given every 12 hours. Brand name Procysbi. Also referred to as extended-release or gastro-resistant mercaptamine bitartrate. Trial name RP103. The dose is based on patient weight and/or body surface area.]<br><br>[Patients may also be receiving supportive care for other physical health consequences of nephropathic cystinosis such as nutritional support, renal support or treatment for diabetes.] |
| **C – Comparator(s)** | Current standard treatment, which is immediate-release mercaptamine bitartrate.<br><br>[Brand name Cystagon]<br><br>Or<br><br>No immediate-release mercaptamine bitartrate<br><br>[Patients may also be receiving supportive care for other physical health consequences of nephropathic cystinosis such as nutritional support, renal support or treatment for diabetes. Patients who are not taking a mercaptamine bitartrate formulation will have high white cell cysteine levels.] |

| | |
|---|---|
| **O – Outcomes** | **<u>Clinical Effectiveness</u>**<br>*Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown.*<br>*Outcomes measured at 3 and 6 months are of particular interest, although longer time points are also of interest.*<br>*<u>Critical to decision making</u>*<br>• **Disease response**<br>*This outcome is important to patients because it reflects how effective the treatment is at preventing disease progression.*<br>[Outcomes measured include white cell cysteine content (target is less than 1nmol hemicystine/mg protein, and this is considered optimal).]<br>• **Treatment adherence**<br>*Treatment adherence is important to patients as it provides an indication of how well the treatment is tolerated. Effective treatment of nephropathic cystinosis requires good compliance to reduce cystine-crystal accumulation in cells. Good adherence can postpone time to developing renal failure requiring dialysis or transplant.*<br>[Examples include, but not limited to, missed doses, self-reported adherence measures e.g. questionnaires or diaries, interview methods.]<br>• **Progression of cystinosis associated renal disease**<br>*This outcome is important, as a goal of effective treatment would be to postpone the physical health consequences of cystinosis such as renal failure requiring dialysis or transplant which would have negative mental and physical health consequences to patients.*<br>[Examples include estimated glomerular filtration rate (eGFR), serum creatinine, need for renal replacement therapy (dialysis), need for renal transplant, progression of chronic kidney disease (CKD)]<br>*<u>Important to decision making</u>*<br>• **Quality of life**<br>*Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making.*<br>[Examples include, but not limited to: Paediatric quality of life scores, interview methods, EQ-5D.]<br>• **Growth Measurements**<br>*Growth measurements such as weight and height are important outcomes to patients and their carers as they can be a marker of treatment success. This is particularly valued by the paediatric patient cohort.*<br>[Examples include height Z score, onset of puberty, the usage of growth hormones.]<br>• **Activities of daily living (ADLs)**<br>*ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.* |

| | |
|---|---|
| | ADLs can be measured using assessments such as:<br>o Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal)<br>o ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL)<br>o Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work or school and other activities).]<br>• **Progression of non-renal cystinosis associated disease**<br>*This outcome is important, as a goal of effective treatment would be to postpone the physical health consequences of cystinosis such as diabetes, hypothyroidism, muscle wasting and central nervous system involvement. To postpone or reduce the development of these complications would be valuable to patients as it would indicate an improvement in their overall health.*<br>[The most important examples of this include patient or clinician reported muscle wasting and central nervous system involvement. Other examples may be serum TSH, serum HbA1c.]<br>• **<u>Safety</u>**<br>*These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.*<br>Examples include, but not limited to:<br>o Frequency of adverse events e.g. gastrointestinal disturbance, halitosis, particularly those that lead to a change in formulation.<br>o Frequency of grade 3 or 4 adverse events<br>o Adverse events leading to discontinuation.<br>o Toxicity<br><br>**<u>Cost effectiveness</u>** |
| **Inclusion criteria** | |
| **Study design** | Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies.<br>If no higher-level quality evidence is found, case series can be considered. |
| **Language** | English only |
| **Patients** | Human studies only |
| **Age** | All ages |
| **Date limits** | 2012 – 2024 |
| **Exclusion criteria** | |

| | |
|---|---|
| **Publication type** | Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, and pre-prints |
| **Study design** | Case reports, resource utilisation studies |

# Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 12 years. Conference abstracts, non-systematic reviews, narrative reviews, case reports, commentaries, letters, editorials, guidelines, and pre-prints were excluded.

Search dates: 01 January 2012 and 26 March 2024

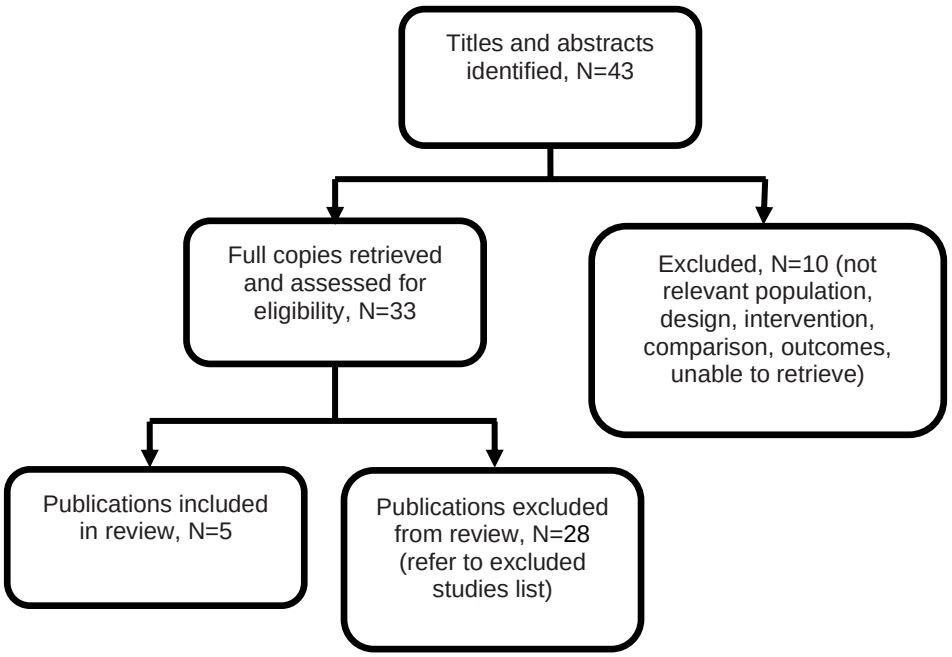
Medline search strategy

| | |
|---|---|
| 1 | Cysteamine/ |
| 2 | (mercaptamine bitartrate or mercamine bitartrate or cysteamine or procysbi).ti,ab,kf. |
| 3 | 1 or 2 |
| 4 | Cystinosis/ |
| 5 | cystinosis.ti,ab,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | (comment or editorial or letter).pt. or case report.ti. |
| 9 | 7 not 8 |
| 10 | exp animals/ not humans/ |
| 11 | 9 not 10 |
| 12 | limit 11 to (english language and yr="2012 -Current") |

# Appendix C Evidence selection

The literature searches identified 43 references. These were screened using their titles and abstracts and 33 references were obtained in full text and assessed for relevance. Of these, four papers and one correction to one of the papers are included in the evidence summary. The remaining 28 references were excluded and are listed in Appendix D.

**Figure 1- Study selection flow diagram**




**References submitted with Preliminary Policy Proposal**

| Reference | Paper selection - decision and rationale if excluded |
|---|---|
| Gaillard S, Roche L, Lemoine S, et al. Adherence to cysteamine in nephropathic cystinosis: A unique electronic monitoring experience for a better understanding. A prospective cohort study: CrYSTobs. Pediatric nephrology. 2021;36(3):581-58 | Included |
| Langman CB, Greenbaum LA, Sarwal M, et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. Clinical journal of the American Society of Nephrology: CJASN. 2012;7(7):1112-1120 | Included |
| Langman CB, Greenbaum LA, Grimm P, et al. Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate. The Journal of pediatrics. 2014;165(3):528-533 e521 | Included |

# Appendix D Excluded studies table

| Study reference | Reason for exclusion |
|---|---|
| Ahlenstiel-Grunow T, Kanzelmeyer NK, Froede K, Kreuzer M, Drube J, Lerch C, Pape L. Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study. Pediatr Nephrol. 2017;32(1):91-7. | Retrospective case series in 12 children. Outcomes for switch from IR to DR mainly presented as individual data and graphical representations and does not provide additional evidence to higher level (prospective) evidence identified that reports in scope outcomes. Outcome data not reported on activities of daily living or progression of non-renal cystinosis associated disease. |
| Ahmad Z, Shatha HA, Sameh H. Impact of age at starting cysteamine therapy on serum chitotriosidase in cystinotic iraqi children. Medico-Legal Update. 2020;20(4):911-6. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Beinart N, Hackett RA, Graham CD, Weinman J, Ostermann M. Mood and illness experiences of adults with cystinosis. Ren Fail. 2015;37(5):835-9. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Bertholet-Thomas A, Claramunt-Taberner D, Gaillard S, Deschenes G, Sornay-Rendu E, Szulc P, et al. Teenagers and young adults with nephropathic cystinosis display significant bone disease and cortical impairment. Pediatr Nephrol. 2018;33(7):1165-72. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Besouw M, Tangerman A, Cornelissen E, Rioux P, Levtchenko E. Halitosis in cystinosis patients after administration of immediate-release cysteamine bitartrate compared to delayed-release cysteamine bitartrate. Mol Genet Metab. 2012;107(1-2):234-6. | Follow-up to crossover RCT (Langman et al 2012); adverse events reported in original RCT. |
| Besouw MTP, Van Dyck M, Francois I, Van Hoyweghen E, Levtchenko EN. Detailed studies of growth hormone secretion in cystinosis patients. Pediatr Nephrol. 2012;27(11):2123-7. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Bjerre A, Aase SA, Radtke M, Siva C, Gudmundsdottir H, Forsberg B, et al. The effects of transitioning from immediate-release to extended-release cysteamine therapy in Norwegian patients with nephropathic cystinosis: a retrospective study. Pediatr Nephrol. 2023;38(11):3671-9. | Retrospective case series (n=10 patients), reporting outcomes for switch from IR to DR mercaptamine and does not provide additional evidence to higher level (prospective) evidence identified that reports in scope outcomes. Outcome data not reported on activities of daily living or progression of non-renal cystinosis associated disease. |
| Brodin-Sartorius A, Tete MJ, Niaudet P, Antignac C, Guest G, Ottolenghi C, et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. Kidney Int. 2012;81(2):179-89. | Intervention out of scope - IR mercaptamine not DR mercaptamine. |
| Emma F, Hoff WV, Hohenfellner K, Topaloglu R, Greco M, Ariceta G, et al. An international cohort study spanning five decades assessed outcomes of nephropathic cystinosis. Kidney Int. 2021;100(5):1112-23. | Intervention out of scope - IR mercaptamine not DR mercaptamine. |
| Frankel AM, Trauner DA. Visual and verbal learning and memory in cystinosis. Brain Cogn. 2019;135:103578. | Unclear whether intervention is DR mercaptamine - out of scope. |

| Study reference | Reason for exclusion |
|---|---|
| Gultekingil Keser A, Topaloglu R, Bilginer Y, Besbas N. Long-term endocrinologic complications of cystinosis. Minerva Pediatr. 2014;66(2):123-30. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Hohenfellner K, Niesl C, Haffner D, Oh J, Okorn C, Palm K, et al. Beneficial effects of starting oral cysteamine treatment in the first 2 months of life on glomerular and tubular kidney function in infantile nephropathic cystinosis. Mol Genet Metab. 2022;136(4):282-8. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Kasimer RN, Langman CB. Adult complications of nephropathic cystinosis: a systematic review. Pediatr Nephrol. 2021;36(2):223-36. | Systematic review including cohort studies and case studies; unclear whether intervention was DR mercaptamine. |
| Klank S, van Stein C, Gruneberg M, Ottolenghi C, Rauwolf KK, Grebe J, et al. Enteric-Coated Cysteamine Bitartrate in Cystinosis Patients. Pharmaceutics. 2023;15(7):29. | Retrospective analysis reporting on one PICO clinical outcome (disease response) and safety after a single dose of IR mercaptamine (n=17) versus enteric release mercaptamine (n=6). These outcomes were reported by higher level (prospective) evidence. Outcome data not reported on activities of daily living or progression of non-renal cystinosis associated disease. |
| Lashilola S, Xu W, Azimpour K, McCarthy M, Carlot S, Game D, van der Voort J. Impact of compliance to oral cysteamine treatment on the costs of Kidney failure in patients with nephropathic cystinosis in the United Kingdom. BMC Nephrol. 2023;24(1):351. | Cost-effectiveness study based on retrospective cohort assessing patients treated with IR mercaptamine - intervention out of scope. |
| Medic G, van der Weijden M, Karabis A, Hemels M. A systematic literature review of cysteamine bitartrate in the treatment of nephropathic cystinosis. Curr Med Res Opin. 2017;33(11):2065-76. | Systematic review of in and out of scope studies. In scope studies included in this evidence review. |
| Nesterova G, Williams C, Bernardini I, Gahl WA. Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy. Pediatr Nephrol. 2015;30(6):945-51. | Intervention out of scope - IR mercaptamine not DR mercaptamine. |
| Niesl C, Boulesteix AL, Oh J, Palm K, Schlingmann P, Wygoda S, et al. Relationship between age at initiation of cysteamine treatment, adherence with therapy, and glomerular kidney function in infantile nephropathic cystinosis. Mol Genet Metab. 2022;136(4):268-73. | Unclear whether intervention is DR mercaptamine - out of scope. |
| O'Connell N, Oh J, Arbeiter K, Buscher A, Haffner D, Kaufeld J, et al. Patients With Infantile Nephropathic Cystinosis in Germany and Austria: A Retrospective Cohort Study. Front Med (Lausanne). 2022;9:864554. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Pache de Faria Guimaraes L, Seguro AC, Shimizu MH, Lopes Neri LA, Sumita NM, de Braganca AC, et al. N-acetyl-cysteine is associated to renal function improvement in patients with nephropathic cystinosis. Pediatr Nephrol. 2014;29(6):1097-102. | Intervention out of scope - IR mercaptamine not DR mercaptamine. |
| Sadek SA, El-Tantawy A, Nasr M. Infantile nephropathic cystinosis: Case series and review of literature. Kuwait Medical Journal. 2013;45(1):55-9. | Intervention out of scope - IR mercaptamine not DR mercaptamine. |

| Study reference | Reason for exclusion |
|---|---|
| Servais A, Saitovitch A, Hummel A, Boisgontier J, Scemla A, Sberro-Soussan R, et al. Central nervous system complications in adult cystinosis patients. J Inherit Metab Dis. 2020;43(2):348-56. | Intervention out of scope - IR mercaptamine not DR mercaptamine. |
| Sikora P, Grenda R, Kowalczyk M, Kiec-Wilk B, Bienias B, Rubik J, et al. Nephropathic cystinosis in Poland: a 40-year retrospective study. Pol Arch Intern Med. 2022;132(11):25. | Unclear whether intervention is DR mercaptamine - out of scope. |
| van Rijssel AE, Knuijt S, Veys K, Levtchenko EN, Janssen MCH. Swallowing dysfunction in patients with nephropathic cystinosis. Mol Genet Metab. 2019;126(4):413-5. | Unclear whether intervention is DR mercaptamine - out of scope. |
| van Stein C, Klank S, Gruneberg M, Ottolenghi C, Grebe J, Reunert J, et al. A comparison of immediate-release and delayed-release cysteamine in 17 patients with nephropathic cystinosis. Orphanet J Rare Dis. 2021;16(1):387. | Retrospective analysis (n=17 patients) reporting on one PICO clinical outcome (disease response) and safety after a single dose of DR cysteamine versus single dose of IR cysteamine. These outcomes were reported by higher level (prospective) evidence. Outcome data not reported on activities of daily living or progression of non-renal cystinosis associated disease. |
| Veys KRP, Elmonem MA, Van Dyck M, Janssen MC, Cornelissen EAM, Hohenfellner K, et al. Chitotriosidase as a Novel Biomarker for Therapeutic Monitoring of Nephropathic Cystinosis. J Am Soc Nephrol. 2020;31(5):1092-106. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Vill K, Muller-Felber W, Landfarth T, Koppl C, Herzig N, Knerr C, et al. Neuromuscular conditions and the impact of cystine-depleting therapy in infantile nephropathic cystinosis: A cross-sectional analysis of 55 patients. J Inherit Metab Dis. 2022;45(2):183-91. | Unclear whether intervention is DR mercaptamine - out of scope. |
| Viltz L, Trauner DA. Effect of age at treatment on cognitive performance in patients with cystinosis. J Pediatr. 2013;163(2):489-92. | Unclear whether intervention is DR mercaptamine - out of scope. |

# Appendix E Evidence table

For abbreviations see list after table

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| **Gaillard S, Roche L, Lemoine S, Deschenes G, Morin D, Vianey-Saban C, et al. Adherence to cysteamine in nephropathic cystinosis: A unique electronic monitoring experience for a better understanding. A prospective cohort study: CrYSTobs. Pediatr Nephrol. 2021;36(3):581-9.**<br>**Study location**<br>France (3 centres)<br>**Study type**<br>Prospective cohort study (CrYSTobs)<br>**Study aim**<br>To assess adherence to SA or DR formulation of oral cysteamine in patients with nephropathic cystinosis<br>**Study dates**<br>December 2011 to September 2014 | Patients with confirmed nephropathic cystinosis<br>**Inclusion criteria**<br>Patients aged >4 years with confirmed nephropathic cystinosis (defined by leukocyte cystine levels at diagnosis and mutation analysis of *CTNS* gene, if available); receiving oral cysteamine [females of potential childbearing age were required to have a negative pregnancy test or accept effective birth control if sexually active]<br>**Exclusion criteria**<br>Patients with known hypersensitivity to cysteamine and penicillamine; females who were nursing, planning a pregnancy, known or suspected to be pregnant, or with a | **Interventions**<br>DR cysteamine every 12 hours: 25 mg or 75 mg capsules at a dose initiation of 70% of total daily dose of SA cysteamine; median (range) daily dosage per BSA 1.06 (0.56 to 1.42) mg/m$^2$/day<br>**Comparators**<br>SA cysteamine every 6 hours: 50 mg or 150 mg capsules; median (range) daily dosage per BSA 1.29 (0.97 to 1.64) mg/m$^2$/day<br>Ten (59%) patients had received kidney transplant, and 2 (12%) were under kidney replacement therapy (haemodialysis) at inclusion. The authors did not report on other concomitant treatments<br>Treatment duration: 12 months | Follow-up: 12 months<br>**Critical outcomes**<br>**Disease response**<br>Defined as leukocyte cystine levels (nmol hemicystine/mg protein), median (range)[34]<br>*All patients*<br>Baseline (n=16): 0.3 (0.1 to 2.5)<br>12 months follow-up (n=17): 1.1 (0.3 to 2.7), i.e. above the optimal target of <1 nmol hemicystine/mg protein<br>Statistical measures were not reported<br>Defined as individual percentage of visits with leukocyte cystine levels ≤1 nmol hemicystine/mg protein, median (range)[35]<br>*All patients*<br>12 months follow-up (n=17): 60% (0% to 100%)<br>**Treatment adherence** | This study was appraised using the JBI checklist for cohort studies.<br>1. Unclear<br>2. NA<br>3. Yes<br>4. Unclear<br>5. Unclear<br>6. No<br>7. Yes for objective measure; no for subjective measure<br>8. Yes<br>9. Yes<br>10. NA<br>11. No<br>**Other comments:**<br>This prospective cohort study recruited a small number of participants with confirmed nephropathic cystinosis who were receiving cysteamine treatment at study enrolment. No attempts were made to identify confounding factors or implement strategies to deal with them. It was unclear whether baseline characteristics were similar |

[34] Individual average of leukocyte cystine levels over the year.
[35] The PICO document states that the target white cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | positive urinary pregnancy test<br>**Total sample size**<br>N=17<br>**No. of participants in each treatment group**<br>DR cysteamine: n=17 [Including 4 patients who received SA cysteamine at study inclusion but then switched to DR cysteamine after 26 to 91 days]<br>SR cysteamine: n=4<br>**Baseline characteristics**<br>Male, n (%): 7 (41.2)<br>Age (years), median (range)<br>13.9 (5.4 to 33)<br>eGFR (ml/min per 1.73 $m^2$), median (range)<br>All patients (n=17): 61.5 (7.9 to 132.2) | | Adherence score[36] [0 to 2[37]] measured using electronic caps (MEMs®)[38], median (range)<br>DR cysteamine (n=17): 1.8 (0.1 to 2)<br>SA cysteamine (n=4): 0.5 (0.3 to 1)<br>Statistical measures were not reported<br>Adherence level (%)[39] measured using electronic caps (MEMs®), median (range)<br>*Good adherence (score 2):*<br>DR cysteamine (n=17): 88 (1 to 99)<br>SA cysteamine (n=4): 2 (0 to 22)<br>*Partial or good adherence (score 1 or 2)*<br>DR cysteamine (n=17): 91 (5 to 99)<br>SA cysteamine (n=4): 43 (27 to 78)<br>The authors reported that 3 of 4 patients initially receiving SA cysteamine reported higher partial or good adherence scores when receiving DR cysteamine (74%, 75% and 92%) compared to SA cysteamine (27%, 52% and 78%). The fourth patient had similar adherence scores during DR and SA | between patients initially treated with SA cysteamine and patients treated with DR cysteamine as these details were not reported separately. The authors stated that the 4 patients who received SA cysteamine at study inclusion switched to DR cysteamine mainly due to participation in a trial that administered DR cysteamine.<br>Most patients had received previous kidney transplant or were receiving kidney dialysis at study enrolment, and a proportion of patients did not have optimal leukocyte cystine levels (i.e. ≤1 nmol hemicystine/mg protein) at baseline, as indicated by the range in levels (i.e. 0.1 to 2.5 nmol hemicystine/mg protein).<br>Individual adherence scores were described narratively and presented as figures. Overall, adherence profiles were similar (homogeneous) for patients aged 5 to 13 years, but different (heterogeneous) for patients aged 14 to 33 years, decreasing with age.<br>All patients completed the study. |

[36] Individual average of daily adherence scores.
[37] Good adherence (score 2); partial adherence (score 1); poor adherence (score 0). Scores were defined according to the number of intakes per 24 hours and the length of delay between intake and the theoretical action time for each formulation of cysteamine (i.e. 12 or 6 hours)
[38] Electronic caps (MEMs®) were adapted to existing bottles of cysteamine. Electronic monitoring is a method for compiling drug dosing histories, integrating a small microcircuit into drug packages and recording the time and date (i.e. opening) whenever it detects that a dose of drug is removed from the bottle.
[39] Individual percentage of days at the corresponding score level.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | Native kidney function (n=5): 63.3 (40 to 90.6) for 4 patients<br>Kidney transplant (n=10): 72.2 (22.4 to 132.2) for 9 patients<br>Kidney dialysis (n=2): 9.7 (7.9 to 11.5) for both patients | | cysteamine treatment (40% and 35%, respectively)<br>Statistical measures were not reported<br><u>Subgroup analysis – median (range) percentage of days with good adherence score</u><br>≤11 years old: 89 (80 to 99)<br>>11 years old: 68 (1 to 99)<br>Statistical measures were not reported<br><u>Self-reported adherence, median (range)</u>[40]<br>*All patients*<br>12 months follow-up (n=17): 9 (4 to 10)<br>**Progression of cystinosis associated renal disease**<br><u>eGFR</u><br>The authors stated that *"GFR remained stable over the year in our cohort of patients"*; no further details were reported | The authors did not report statistical measures for any outcomes.<br>**Source of funding:**<br>Ministry of Health. |
| **Langman CB, Greenbaum LA, Sarwal M, Grimm P, Niaudet P, Deschenes G, et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in** | Patients with confirmed nephropathic cystinosis<br>**Inclusion criteria**<br>Adults or children who had their own kidneys and an eGFR >30 | **Interventions**<br>DR cysteamine bitartrate capsule taken daily every 12 hours: 25 mg or 75 mg capsules (mean dose not reported) | Follow-up: 3-week crossover periods<br>**Critical outcomes**<br>**Disease response** | This study was appraised using the JBI checklist for RCTs.<br>1. Unclear<br>2. No<br>3. Unclear<br>4. No |

[40] Individual average of self-reported adherence over the year. Patients evaluated their adherence answering the following question on a visual analogical scale: *"How do you evaluate your adherence to cysteamine?"* at each study visit; no further details were provided, but for we have assumed this was measured using a score of 1 to 10.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| **nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. Clin J Am Soc Nephrol. 2012;7(7):1112-20.**<br>**Study location**<br>USA (3 centres), France and the Netherlands (5 centres)<br>**Study type**<br>Open-label, crossover RCT<br>**Study aim**<br>To assess whether WBC cystine depletion is similar between DR cysteamine bitartrate (RP103) versus IR cysteamine bitartrate (Cystagon) in patients with nephropathic cystinosis and their own kidneys<br>**Study dates**<br>Not stated | ml/min per 1.73 $m^2$ body surface area; able to swallow their typically administered IR cysteamine bitartrate capsules intact[41]<br>**Exclusion criteria**<br>None stated<br>**Total sample size**<br>N=43; patients crossed over from treatment with DR cysteamine bitartrate to IR cysteamine bitartrate, or vice versa<br>**Baseline characteristics**<br>Male, n (%): 24 (56)<br>Age (years)<br>All patients, mean (SD): 11.7 (4.2) | **Comparators**<br>IR cysteamine bitartrate capsule taken daily every 6 hours<br>Daily IR cysteamine bitartrate dose (mg/day), mean (SD): 1849 (536)<br>Daily IR cysteamine bitartrate dose (mg/kg), mean (SD): 55.8 (15.2)<br>During the run-in period, 18/38 (47%) patients in the per protocol study analysis took PPIs and continued them during the IR cysteamine bitartrate treatment period. 13/18 (72%) patients using PPIs during the IR cysteamine bitartrate treatment period stopped them during the DR cysteamine bitartrate treatment period, and no | Defined as WBC cystine level (nmol hemicystine/mg protein), LSM[43] (SEM)[44]<br>DR cysteamine bitartrate (n=41): 0.70 (0.19), optimal at ≤1 nmol hemicystine/mg protein<br>IR cysteamine bitartrate (n=41): 0.97 (0.19)[45], optimal at ≤1 nmol hemicystine/mg protein but 3 patients had a mean WBC cystine level >2 nmol hemicystine/mg protein and were considered *"not well controlled"*<br>*Difference between treatment groups, LSM (SEM; 95.8% CI):*[46] -0.27 (0.36; -0.63 to 0.09[47]); p<0.001[48]<br>**Important outcomes**<br>**Safety** | 5. No<br>6. No<br>7. No<br>8. Yes<br>9. Yes<br>10. Yes<br>11. Yes<br>12. Unclear<br>13. Unclear<br>**Other comments:**<br>This 3-week crossover RCT included patients who were well controlled on IR cysteamine bitartrate. It was unclear whether the RCT used true randomisation to assign participants to treatment groups as limited details were provided. Treatment allocation was not concealed as participants continued with their usual IR cysteamine bitartrate or switched to DR cysteamine bitartrate. Baseline characteristics were reported for all |

[41] Prior to study commencement, patients had to be taking a stable dose of IR cysteamine which was considered by the site investigator as sufficient to maintain their WBC cystine level at ≤2.0 nmol hemicystine/mg protein.
[43] A mixed-effects statistical model was used to calculate least squares mean; no further details were provided.
[44] A correction (Anonymous 2013) to the published article was issued which stated that *"a systematic error had been made in the calculation of the final white blood cell cystine concentrations (WBC [cystine]) in all samples, resulting in an approximate 25% lower value than that reported for all patients in all arms of the study. Using the revised WBC [cystine] would have allowed one additional patient (39 of 43) to be accounted for in the data analysis rather than the 38 of 43 included in the original manuscript, based on the entry criteria specified in the article".* The correction stated that this did not alter the results reported in the publication.
[45] Three patients had a 3-day average WBC cystine level >2 nmol hemicystine/mg protein during one of the IR cysteamine bitartrate treatment periods and were therefore considered not to be well controlled.
[46] The authors stated that they used the 95.8% CI instead of 95% CI to take into account a sample size re-estimation calculation that was performed after 20 patients were enrolled.
[47] The upper end of the confidence interval (0.09) was lower than the 0.3 nmol hemicystine/mg protein noninferiority limit that the authors defined a priori.
[48] The outcome of noninferior WBC cystine levels was achieved at a lower average daily dose of DR cysteamine (1513; SEM 477 mg/day) compared with IR cysteamine (1801; SEM 511 mg/day). On average, the total daily steady-state dose of DR cysteamine in patients was 82% of their established incoming dose of IR cysteamine.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | Children (aged between 2 and ≤12 years), n: 27<br>Adolescents (aged between 12 and ≤21 years), n: 15<br>Adults (aged >21 years), n: 1<br>eGFR (ml/min per 1.73 $m^2$), mean (SD): 86 (34)<br>WBC cystine (nmol hemicystine/mg protein), mean (SD): 0.66 (0.34)<br>WBC cystine (<1 nmol hemicystine/mg protein), n (%): 37 (86) | other study patients started them during the DR cysteamine bitartrate treatment period[42]<br>Treatment duration: 2-week run-in period; 3 weeks for each treatment period | Total number of AEs[49, 50]<br>DR cysteamine bitartrate (n=43): 69; 31 were gastrointestinal disorders [23 were considered treatment-related and 8 not treatment-related]<br>IR cysteamine bitartrate (n=41): 25; 11 were gastrointestinal disorders [9 were considered treatment-related and 3 not treatment-related]<br>Number of patients experiencing at least one SAE<br>DR cysteamine bitartrate (n=43): 6 (one gastrointestinal SAE was considered to be potentially related to DR cysteamine bitartrate treatment; the remaining SAEs were not treatment-related)[51]<br>IR cysteamine bitartrate (n=41): 1, which was not considered to be treatment-related | participants and it was therefore unclear whether treatment groups were similar at baseline. The RCT was open label as the authors stated that blinding was not possible due to differences in the two treatments in terms of dosing schedule and different strengths of capsules, but as the outcomes were measured objectively, the potential risk of bias would be minimal Treatment groups were treated differently in terms of PPI use, whereby PPIs were intended to be discontinued during the DR cysteamine bitartrate treatment period but permitted during the IR cysteamine bitartrate treatment period.<br>It was unclear whether the sample size calculation reported by the authors was met, and therefore whether the study was underpowered.<br>Prior to treatment randomisation, the trial had a 2-week run-in period, at the beginning of which the trough cysteamine concentration and the highest (peak) WBC cystine level |

[42] Overall, PPIs were taken 453 times during the IR cysteamine treatment periods. Five patients took PPIs for a total of 58 times during the DR cysteamine treatment period, representing an 87% reduction in PPI use during identical time periods.
[49] Any AE starting and resolving in one of the crossover periods was counted once for that period.
[50] The number of events were also reported separately for the following AEs: metabolism and nutrition disorders; nervous system disorders; cardiac disorders; general disorders and administration site conditions; infections and infestations; skin and subcutaneous tissue disorders; vascular disorders; musculoskeletal and connective tissue disorders; respiratory, thoracic, and mediastinal disorders; injury, poisoning, and procedural complications; investigations; ear and labyrinth disorders; eye disorders; psychiatric disorders.
[51] The authors reported in the narrative that the five remaining SAEs were gastrointestinal related, but the figures in the table presented suggest that there were two additional SAEs related to gastrointestinal disorders, one metabolism and nutrition disorders, and two related to injury, poisoning, and procedural complications.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | | | | were measured in patients every morning over 3 consecutive days. The daily dose of DR cysteamine bitartrate was equal to approximately 70% of the usual dose of IR cysteamine bitartrate. It was unclear whether there was a washout period between treatment periods and if so, whether this was sufficient; the authors stated that outcomes were measured over 3 consecutive days at the end of each 3 week treatment period.<br>ITT analyses were conducted as well as PP; only ITT data are reported in this evidence review. Two related patients withdrew from the study because one had planned orthopaedic surgery, unrelated to the study drugs, and the family decided to withdraw both children related to subsequent travel difficulties. These two patients do not appear to have been included in the ITT analysis for WBC cystine level.<br>The authors reported that the 41 patients who completed the crossover trial were given the opportunity to enrol in an extension study to continue treatment with DR cysteamine bitartrate, of which 40 (97.6%) patients chose to do so. Two patients withdrew from the study (reported to be unrelated to the study). |

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | | | | **Source of funding:**<br>Raptor Pharmaceuticals Inc and the National Centre for Research Resources. |
| **Langman CB, Greenbaum LA, Grimm P, Sarwal M, Niaudet P, Deschenes G, et al. Quality of life is improved and kidney function preserved in patients with nephropathic cystinosis treated for 2 years with delayed-release cysteamine bitartrate. J Pediatr. 2014;165(3):528-33.e1.**<br>**Study location**<br>USA (3 centres), France and the Netherlands (5 centres)<br>**Study type**<br>Prospective, single-arm study (follow on to Langman et al 2012)<br>**Study aim**<br>To evaluate the long-term effects of DR cysteamine bitartrate in terms of quality of life and kidney function on patients with nephropathic cystinosis | **Inclusion criteria**<br>See Langman et al (2012)<br>**Exclusion criteria**<br>None stated<br>**Total sample size**<br>DR cysteamine bitartrate: N=40/41 patients who completed the crossover RCT (Langman et al 2012)<br>**Baseline characteristics**<br>Male, n (%): 23 (57.5)<br>Age (years)<br>All patients, mean (SD): 11.5 (3.6)<br>Children (aged between 6 and ≤12 years), n: 25<br>Adolescents (aged between 12 and ≤21 years), n: 15<br>Adults (aged >21 years), n: 0 | **Interventions**<br>DR cysteamine bitartrate capsule taken daily every 12 hours: total daily dose (mean % of previous IR cysteamine dose) 83.7 (SD 7.9)<br>**Comparators**<br>None<br>Growth hormones were permitted, but no further details were reported<br>Treatment duration: 24 months | Follow-up: 24 months, unless otherwise stated<br>**Critical outcomes**<br>**Disease response**<br>Defined as WBC cystine level (nmol hemicystine/mg protein), mean (SD)<br>Baseline: 0.43 (0.15)<br>At 24 months: 0.55 (0.34)<br>*Mean change from baseline: p=0.38*<br>The authors reported that *"mean WBC (cystine) remained below 1 nmol ½ cystine/mg protein during the entire study"*[52]<br>**Progression of cystinosis associated renal disease**<br>Defined as eGFR (mL/min/1.73m$^2$), mean (SD)<br>Baseline: 63 (25)<br>At 24 months: 57 (25)<br>*Mean change from baseline: p=0.32* | This study was appraised using the JBI checklist for case series.<br>1. Yes<br>2. Yes<br>3. Yes<br>4. NA<br>5. No<br>6. Yes<br>7. Yes<br>8. Yes<br>9. No<br>10. Yes<br>**Other comments:**<br>This was a prospective, single-arm 2-year follow-up study assessing the long-term effects of DR cysteamine bitartrate in 40 of 41 well controlled patients who had completed a crossover trial comparing DR versus IR cysteamine bitartrate.<br>1 patient withdrew from the study at 21 months due to a decline in eGFR and the need for maintenance dialysis. |

[52] ½ cystine/mg protein also referred to as hemicystine/mg protein. The PICO document states that the target which cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| **Study dates**<br>Not stated | WBC cystine (nmol hemicystine/mg protein), mean (SD): 0.79 (1.68)<br>WBC cystine (≤1 nmol hemicystine/mg protein), n (%): 34 (85) | | Defined as need for renal transplant<br>1 patient underwent renal transplant at 17 months<br><br>Defined as need for renal replacement therapy (dialysis)<br><br>eGFR declined in 1 patient who required maintenance dialysis<br><br>**Important outcomes**<br><br>**Quality of life**<br><br>Percentage change in PedsQL[53] from baseline, intercept (LSM, SEM not reported)[54]<br><br>*Unclear follow-up*<br>Physical: 6.62; p=0.160<br>Emotional: 6.62; p=0.136<br>Social: 11.23; p=0.049<br>School: 14.27; p=0.004<br>Total: 5.99; p=0.048<br><br>Percentage change in PedsQL from baseline, slope[55]<br><br>Physical: 0.302; p=0.054<br>Emotional: 0.019; p=0.890<br>Social: 0.492; p=0.201 | Limited data were provided on site/clinic demographic information.<br><br>Longitudinal data were analysed using a mixed model ANOVA, which enable a variable number of repeat evaluations to be made per participant and took into account the variability specific to each participant.<br><br>The authors hypothesised that adherence was greater in their study of DR cysteamine bitartrate compared to IR cysteamine bitartrate observational studies, but this was not formally assessed.<br>**Source of funding:**<br>See Langman et al (2012). |

[53] PedsQL is a paediatric quality of life questionnaire assessing four areas of functionality: physical, emotional, social, and school. Details on the PedsQL scoring algorithm were not reported, but higher values indicate better health related quality of life.
[54] The intercept value (LSM) represents the change from the value under IR cysteamine from the prior three week crossover RCT (Langman et al 2012).
[55] The slope represents the change from baseline to 24 months during treatment with DR cysteamine in the single-arm follow-up study to the crossover RCT.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | | | School: 0.126; p=0.598<br>Total: 0.184; p=0.072<br><br>**Growth measurements**[56]<br><br>Measured as height Z-score, mean (SD)[57]<br><br>Baseline: -1.15 (-0.93)<br>At 24 months: -1.21 (-0.96)<br><br>*Mean change from baseline: p=0.46*<br><br>Measured using BMI (kg/m$^2$), mean (SD)<br><br>Baseline: 18.2 (3.1)<br>At 24 months: 18.3 (3.2)<br><br>*Mean change from baseline: p=0.27*<br><br>**Safety**<br><br>Number of patients experiencing at least 1 AE, n (%)<br><br>40 (100); all were considered to be treatment-related<br><br>Number of patients experiencing gastrointestinal disorders (the most commonly occurring AE), n (%) | |

[56] The authors stated that *"no patient using growth hormone during the study were evaluated for growth change with the other members of the study",* but no further details were reported.
[57] Height Z-score for age was calculated using the Centres of Diseases Control and Prevention growth charts.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | | | 35 (87.5)[58] | |
| **Vaisbich MH, Caires Ferreira J, Price H, Young KD, Sile S, Checani G, Langman CB. Cysteamine bitartrate delayed-release capsules control leukocyte cystine levels and promote statural growth and kidney health in an open-label study of treatment-naive patients <6 years of age with nephropathic cystinosis. JIMD rep. 2022;63(1):66-79.**<br>**Study location**<br>Brazil and the USA<br>**Study type**<br>Case series<br>**Study aim**<br>To assess the safety and effectiveness of long-term repeat dosing of DR cysteamine on WBC cystine concentrations in children | Children with documented nephropathic cystinosis<br>**Inclusion criteria**<br>Patients aged <6 years with documented diagnosis of cystinosis with no clinically significant change in liver function tests (i.e. 1.5 times ULN for ALT and AST, and/or 1.5 times ULN for total bilirubin) within 6 months prior to screening; no clinically significant change in renal function (i.e. eGFR within 6 months prior to screening and an eGFR >20 ml/min/1.73 $m^2$); required haemoglobin level was >10 g/dl at screening<br>**Exclusion criteria** | **Interventions**<br>DR cysteamine administered through intragastric methods, dietary or orally every 12 hours: recommended target dose 1 g/$m^2$/day<br>Final dose (n=14): 200 to 600 mg per day[59]<br>**Comparators**<br>None<br>All patients (100%) reported using at least one concomitant treatment, which was started or continued after the first dose of study drug. The most frequently used concomitant treatments included: potassium chloride, phosphorus, calcitriol, and sodium bicarbonate (>70% of patients each); ferrous sulphate, ergocalciferol, omeprazole, and ranitidine (>40% of patients each); and sodium chloride (electrolyte | Follow-up: at interim timepoints up to18 months and/or at study exit (timeframe not clear)[60]<br>Outcomes reported for n=15 children, unless otherwise stated<br>**Critical outcomes**<br>**Disease response**<br>Defined as WBC cystine concentration (nmol hemicystine/mg protein), mean (SD)<br>Baseline (n=15): 3.2 (3.0)<br>Study exit (timeframe not clear) (n=13): 0.8 (0.8)[61], the authors reported this was a *"clinically meaningful"* decrease (i.e. improvement), but the definition of a clinically meaningful effect size was not provided<br>*Mean change from baseline to study exit: p=0.04*<br>Not reported at other timepoints<br>Proportion of participants who reached WBC cystine <1 nmol hemicystine/mg protein, n/N (%)[62] | This study was appraised using the JBI checklist for case series.<br>1. Yes<br>2. Yes<br>3. Yes<br>4. No<br>5. No<br>6. Yes<br>7. Yes<br>8. Yes<br>9. No<br>10. Yes for one outcome<br>**Other comments:**<br>This was a small study including treatment naïve children treated with DR cysteamine for nephropathic cystinosis. The study initially included any patient with untreated cystinosis, but following the enrolment of 4 patients, 2 aged >6 years old (9 and 22 years old) and 2 aged <6 years old, the authors amended the protocol to include only patients <6 years old to satisfy a |

[58] In terms of specific symptoms, emesis was experienced by 28 (70.0%) patients, followed by headache in 14 (35.0%) patients, upper respiratory tract symptoms in 9 (22.5%) patients, and diarrhoea in 8 (20.0%) patients.
[59] One patient received only one dose of DR cysteamine.
[60] Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.
[61] WBC cystine concentrations were reported for baseline and study exit only (timeframe not clear), data for other timepoints were only presented graphically.
[62] The PICO document states that the target white cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| who were naïve to treatment with cysteamine<br>**Study dates**<br>Not stated | Patients with any of the following: history of active inflammatory bowel disease or prior resection of the small intestine; heart disease; active bleeding disorder within 90 days prior to screening; malignant disease within 2 years prior to screening; kidney transplant, or using dialysis at time of trial<br>**Total sample size**<br>N=15<br>**Baseline characteristics**<br>Male, n (%): 8 (53.3)<br>Age (years), mean (SD; range): 2.2 (1.0; 1.0 to 4.5)<br>Ethnicity (white), n (%): 11 (73.3)<br>The diagnosis of nephropathic cystinosis was based on Fanconi syndrome associated with corneal cystine crystals in all 15 | solution), levothyroxine, cholecalciferol, potassium citrate, magnesium sulphate, paracetamol, calcium carbonate, erythropoietin, sodium chloride (nasal preparation), ondansetron, and osmotan. The most frequent procedure was gastrostomy or reinsertion of G-tube (three patients)<br>Treatment duration: between 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months | Baseline: 3/15 (20.0)<br>Study exit (timeframe not clear): 10/13 (76.9)<br>Not reported at other timepoints, and statistical measures not reported<br>**Progression of cystinosis associated renal disease**<br>Defined as eGFR (ml/min/1.73m$^2$),[63] mean (SD)[64]<br>Baseline (n=15): 55.93 (22.43)<br>Week 2 (n=NR): 57.62 (19.35)<br>Week 6 (n=NR): 55.43 (17.41)<br>Week 10 (n=NR): 53.83 (17.72)<br>Month 6 (n=NR): 61.27 (15.47)<br>Month 9 (n=NR): 61.71 (23.43)<br>Month 12 (n=NR): 60.92 (25.63)<br>Month 18 (n=NR): 67.20 (31.17)<br>Study exit (timeframe not clear) (n=14): 63.79 (21.44)<br>*Mean (SD) change from baseline to study exit: 8.14 (15.48 ml/min/1.73m$^2$); statistical measures were not reported*<br>**Important outcomes**<br>**Growth measurements[65]**<br>Defined as Z score standing height, mean (SD) | Food & Drug Administration (FDA) post marketing commitment. The study was carried out in one hospital in the USA and one in Brazil, but no further details were provided.<br>All patients were asked to stop gastric acid-reducing medications at least 12 hours before receiving their first dose of DR cysteamine until the end of the trial, but gastric acid-reducing treatment was permitted for intolerable gastric upset. Growth hormones were not administered. Diet was ad lib without restrictions or required supplementation.<br>**Source of funding:**<br>Horizon Therapeutics plc. |

[63] eGFR was determined using the creatinine-based 'Bedside Schwartz' equation, appropriate for children aged 1 to 18 years of age (i.e. 0.413* [Height (cm) / serum creatinine (mg/dl)]).
[64] The number of patients providing eGFR data were only reported at baseline and study exit (timeframe not clear). Data for remaining timepoints were only presented graphically, and only represented n=10 children, the reason for which was not explained.
[65] Z-scores were based on the Centre for Disease Control and Prevention (CDC) growth data for the general population.

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | patients; genetic testing was performed in 9 patients to confirm diagnosis | | Baseline (n=15): -3.2 (1.6)<br>Week 2 (n=NR): -2.9 (1.5)<br>Week 12 (n=NR): -2.5 (1.5)<br>Month 6 (n=NR): -2.0 (1.7)<br>Month 12 (n=NR): -1.1 (1.9)<br>Month 18 (n=NR): 0.1 (2.1)<br>Study exit (timeframe not clear) (n=15): 0.1 (2.0)<br>Statistical measures were not reported for any timepoint<br><u>Defined as Z score weight, mean (SD)</u><br>Baseline (n=15): -4.0 (2.1)<br>Week 2 (n=NR): -3.9 (2.1)<br>Week 12 (n=NR): -3.3 (2.1)<br>Month 6 (n=NR): -2.8 (2.3)<br>Month 12 (n=NR): -2.2 (1.7)<br>Month 18 (n=NR): -1.3 (2.0)<br>Study exit (timeframe not clear) (n=15): -1.1 (1.8)<br>Statistical measures were not reported for any timepoint<br><u>Defined as Z score BSA, mean (SD)</u><br>Baseline (n=15): -1.8 (1.1)<br>Study exit (timeframe not clear) (n=14): -1.3 (1.1)<br>Not reported at other timepoints<br><u>Defined as Z score BMI, mean (SD)</u><br>Baseline (n=15): -1.0 (1.1) | |

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| | | | Study exit (timeframe not clear) (n=14): -1.2 (1.3)<br>Not reported at other timepoints<br>**Safety**<br><u>Number of patients with any AE (%)</u><br>15 (100); it was unclear whether AEs were treatment-related<br><u>Number of patients with SAEs, n (%)</u><br>12 patients (80.0) had at least one SAE for a total of 36 SAEs, but none were considered to be treatment-related:<br>Gastroenteritis: 5/15 (33.3)<br>Dehydration: 4/15 (26.7)<br>Vomiting: 4/15 (26.7)<br>Electrolyte imbalance: 2/15 (13.3)<br>Gastrostomy: 2/15 (13.3)<br>*"One patient died on Day 17 of study treatment, during the titration period, the patient had four grade 5 SAEs: gastroenteritis, hypovolemic shock, cardiopulmonary failure, and Fanconi syndrome. The patient was hospitalised and died the next day. In the Investigator's assessment, the SAEs were likely related to the underlying cystinosis and not related to the study treatment"* | |

**Abbreviations**

AE: adverse event; ALT: alanine aminotransferase; ANOVA: analysis of variance; AST: aspartate aminotransferase; BMI: body mass index; BSA: body surface area; CI: confidence interval; CTNS gene: Cystinosin gene: DR: delayed-release; eGFR: estimated glomerular filtration rate; FDA: Food and Drug Administration; g: gram; G-tube: gastrostomy tube; IR: immediate-release; ITT: intention-to-treat; kg: kilogram; LSM: least squares mean; MEMs®: medication event monitoring system; ml: millilitre; mg: milligram; min: minute; nmol;

| Study details | Population | Interventions | Study outcomes | Appraisal and funding |
|---|---|---|---|---|
| nanomole; N: number; NA: not applicable; NR: not reported; PedsQL: paediatric quality of life inventory; PP: per protocol; PPI: proton pump inhibitor; RCT: randomised controlled trial; SA: short-acting; SAE: serious adverse event; SD: standard deviation; SEM: standard error of the mean; ULN: upper limit of normal; USA: United States of America; WBC: white blood cell. | | | | |

# Appendix F Quality appraisal checklists

### JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering the treatment blind to treatment assignment?
6. Were treatment groups treated identically other than the intervention of interest?
7. Were outcome assessors blind to treatment assignment?
8. Were outcomes measured in the same way for treatment groups?
9. Were outcomes measured in a reliable way
10. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
11. Were participants analysed in the groups to which they were randomised?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

### JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilised?
11. Was appropriate statistical analysis used?

**JBI Critical Appraisal Checklist for Case Series**

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

# Appendix G GRADE profiles

For abbreviations and footnotes see end of tables

**Table 2: DR mercaptamine bitartrate vs IR mercaptamine bitartrate**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | DR mercaptamine bitartrate | IR mercaptamine bitartrate | Result | | |
| **Disease response (1 RCT)** | | | | | | | | | |
| **WBC cystine levels (nmol hemicystine/mg protein), LSM (SEM) at 3-week crossover [values ≤1 nmol hemicystine/mg protein indicate optimal control]** | | | | | | | | | |
| 1 RCT<br><br>Langman et al 2012 | Very serious limitations[1] | No serious indirectness | Not applicable | Not calculable | 41 | 41 | DR cysteamine bitartrate: 0.70 (0.19)<br>IR cysteamine bitartrate: 0.97 (0.19)[a]<br><br>*Difference between treatment groups, LSM (SEM; 95.8% CI): -0.27 (0.36; -0.63 to 0.09[b]); p<0.001* | Critical | LOW |
| **Treatment adherence (1 prospective cohort study)** | | | | | | | | | |
| **Adherence score[c] measured using electronic caps (MEMs®),[d] median (range) to 12 months [higher values indicate better adherence]** | | | | | | | | | |
| 1 prospective cohort study<br><br>Gaillard et al 2021 | Very serious limitations[2] | Serious indirectness[3] | Not applicable | Not calculable | 17 | 4 | DR cysteamine: 1.8 (0.1 to 2)<br>SA cysteamine: 0.5 (0.3 to 1) | Critical | VERY LOW |
| **Adherence level[e] (%) measured using electronic caps (MEMs®),[d] good adherence (score 2), median (range) to 12 months [higher values indicate better adherence]** | | | | | | | | | |
| 1 prospective cohort study<br><br>Gaillard et al 2021 | Very serious limitations[2] | Serious indirectness[3] | Not applicable | Not calculable | 17 | 4 | DR cysteamine: 88 (1 to 99)<br>SA cysteamine: 2 (0 to 22) | Critical | VERY LOW |
| **Adherence level[e] (%) measured using electronic caps (MEMs®),[d] partial or good adherence (score 1 or 2), median (range) to 12 months [higher values indicate better adherence]** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 prospective cohort study<br><br>Gaillard et al 2021 | Very serious limitations[2] | Serious indirectness[3] | Not applicable | Not calculable | 17 | 4 | DR cysteamine: 91 (5 to 99)<br>SA cysteamine: 43 (27 to 78)<br><br>The authors reported that 3 of 4 patients initially receiving SA cysteamine reported higher partial or good adherence scores when receiving DR cysteamine (74%, 75% and 92%) compared to SA cysteamine (27%, 52% and 78%). The fourth patient had similar adherence scores during DR and SA cysteamine treatment (40% and 35%, respectively) | Critical | VERY LOW |
| **Quality of life (1 prospective single-arm follow-up study)** | | | | | | | | | |
| **Percentage change in PedsQL,[f] intercept (LSM; SEM not reported)[g] to unclear follow-up duration (from three week crossover RCT to treatment with DR cysteamine during the single-arm follow-up study) [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[4] | No serious indirectness | Not applicable | Not calculable | 40 | 40 | Physical: 6.62; *change from baseline (p=0.160)*<br>Emotional: 6.62; *change from baseline (p=0.136)*<br>Social: 11.23; *change from baseline (p=0.049)*<br>School: 14.27; *change from baseline (p=0.004)*<br><br>*Total: 5.99; change from baseline (p=0.048)* | Important | VERY LOW |
| **Safety (1 RCT)** | | | | | | | | | |
| **Total number of AEs at 3-week crossover** | | | | | | | | | |
| 1 RCT<br><br>Langman et al 2012 | Very serious limitations[5] | No serious indirectness | Not applicable | Not calculable | 43 | 41 | DR cysteamine bitartrate: 69 (31 were gastrointestinal disorders, with 23 considered treatment-related and 8 not treatment-related)<br>IR cysteamine bitartrate: 25 (11 were gastrointestinal disorders, with 8 | Important | LOW |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | considered treatment-related and 3 not treatment-related) | | |
| **Number of SAEs at 3-week crossover** | | | | | | | | | |
| 1 RCT<br><br>Langman et al 2012 | Very serious limitations[5] | No serious indirectness | Not applicable | Not calculable | 43 | 41 | DR cysteamine bitartrate: 6 (3 were gastrointestinal disorders, with one considered treatment-related and 2 not treatment-related. One SAE was related to metabolic and nutrition disorders, but not considered to be treatment-related. The remaining 2 SAEs were injury or procedural related and not treatment-related)<br>IR cysteamine bitartrate: 1 (considered to be not treatment-related) | Important | LOW |
| **Abbreviations**<br>AE: adverse event; CI: confidence interval; DR: delayed-release; IR: immediate-release; LSM: least squares mean; MEMs®: medication event monitoring system; mg: milligram; nmol; nanomole; RCT: randomised controlled trial; SA: short-acting; SAE: serious adverse event; SEM: standard error of the mean; WBC: white blood cell. | | | | | | | | | |

*1 Risk of bias: very serious limitations due to unclear randomisation and allocation methods, and uncertainty around whether the two treatment groups were similar at baseline.*
*2 Risk of bias: very serious limitations due to uncertainty as to whether the two treatment groups were similar at baseline, no details on confounding factors or whether strategies were implemented to deal with them, and lack of statistical analyses.*
*3 Indirectness: serious indirectness due to intervention group including four patients who initially received treatment with SA cysteamine before switching to DR cysteamine.*
*4 Risk of bias: serious limitations due to incomplete inclusion of participants.*
*5 Risk of bias: very serious limitations due to unclear randomisation and allocation methods, uncertainty around whether the two treatment groups were similar at baseline and lack of statistical analyses.*

a Three participants had a 3-day average WBC cystine level >2 nmol hemicystine/mg protein during one of the IR cysteamine bitartrate treatment periods and were therefore considered to be *"not well controlled".*
b The authors stated that they used the 95.8% CI instead of 95% CI to take into account a sample size re-estimation calculation that was performed after 20 patients were enrolled. The upper end of the confidence interval (0.09) was lower than the 0.3 nmol hemicystine/mg protein noninferiority limit that the authors defined *a priori*.
c Individual average of daily adherence scores.
d Electronic caps (MEMs®) were adapted to existing bottles of cysteamine. Electronic monitoring is a method for compiling drug dosing histories, integrating a small microcircuit into drug packages and recording the time and date (i.e. opening) whenever it detects that a dose of drug is removed from the bottle.
e Individual percentage of days at the corresponding score level.
f PedsQL is a paediatric quality of life questionnaire assessing four areas of functionality: physical, emotional, social, and school. Details on the PedsQL scoring algorithm were not reported, but higher values indicate better health related quality of life.
g The intercept value (LSM) represents the change from the value during treatment with IR cysteamine from the prior three week crossover RCT with its accompanying p-value for that change.

**Table 3: DR mercaptamine bitartrate vs no comparator**

| QUALITY | | | | | Summary of findings | | | IMPORTANCE | CERTAINTY |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | No of patients | | Effect | | |
| Study | Risk of bias | Indirectness | Inconsistency | Imprecision | DR mercaptamine bitartrate | No comparator | Result | | |
| **Disease response (1 prospective single-arm follow-up study, 1 prospective cohort study, 1 prospective case series)** | | | | | | | | | |
| **Leukocyte cystine levels (nmol hemicystine/mg protein), median (range) to 12 months [values ≤1 nmol hemicystine/mg protein indicate optimal control]** | | | | | | | | | |
| 1 prospective cohort study<br><br>Gaillard et al 2021 | Very serious limitations[1] | Very serious indirectness[2] | Not applicable | Not calculable | 17 | None | Baseline (n=16): 0.3 (0.1 to 2.5)<br>At 12 months (n=17): 1.1 (0.3 to 2.7)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **Visits with leukocyte cystine levels ≤1 nmol hemicystine/mg protein (%), median (range) to 12 months[a]** | | | | | | | | | |
| 1 prospective cohort study<br><br>Gaillard et al 2021 | Very serious limitations[1] | Very serious indirectness[2] | Not applicable | Not calculable | 17 | None | 60 (0 to 100) | Critical | VERY LOW |
| **WBC cystine concentration (nmol hemicystine/mg protein), mean (SD) to study exit (timeframe not clear)[b] [values ≤1 nmol hemicystine/mg protein indicate optimal control]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Serious limitations[3] | Serious indirectness[4] | Not applicable | Not calculable | 13 | None | Baseline (n=15): 3.2 (3.0)<br>Study exit (n=13): 0.8 (0.8 )<br><br>*Mean change from baseline to study exit: p=0.04* | Critical | VERY LOW |
| **Proportion of participants who reached WBC cystine <1 nmol hemicystine/mg protein,[c] n/N (%) to study exit (timeframe not clear)[b] [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 13 | None | Baseline: 3/15 (20.0)<br>Study exit: 10/13 (76.9)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **WBC cystine levels (nmol hemicystine/mg protein), mean (SD) to 24 months [values ≤1 nmol hemicystine/mg protein indicate optimal control]** | | | | | | | | | |

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| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[6] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | Baseline: 0.43 (0.15)<br>At 24 months: 0.55 (0.34)<br><br>*Mean change from baseline to 24 months: p=0.38* | Critical | VERY LOW |
| **WBC cystine levels (<1 nmol hemicystine/mg protein), mean to 24 months [values ≤1 nmol hemicystine/mg protein indicate optimal control]** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Very serious limitations[7] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | The authors reported that *"mean WBC (cystine) remained below 1 nmol ½* [hemi] *cystine/mg protein during the entire study"* | Critical | VERY LOW |
| **Treatment adherence (1 prospective cohort study)** | | | | | | | | | |
| **Self-reported adherence,[d] median (range) to 12 months [higher values indicate better adherence]** | | | | | | | | | |
| 1 prospective cohort study<br><br>Gaillard et al 2021 | Very serious limitations[8] | Very serious indirectness[2] | Not applicable | Not calculable | 17 | None | 9 (4 to 10) | Critical | VERY LOW |
| **Progression of cystinosis associated renal disease (1 prospective single-arm follow-up study, 1 prospective cohort study, 1 prospective case series)** | | | | | | | | | |
| **eGFR (ml/min/1.73m$^2$), mean (SD) to 2 weeks [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): 55.93 (22.43)<br>Week 2 (n=NR): 57.62 (19.35)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **eGFR (ml/min/1.73m$^2$), mean (SD) to 6 weeks [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): 55.93 (22.43)<br>Week 6 (n=NR): 55.43 (17.41) | Critical | VERY LOW |

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|---|---|---|---|---|---|---|---|---|---|
| Vaisbich et al 2022 | | | | | | | Statistical measures were not reported | | |
| **eGFR (ml/min/1.73m$^2$), mean (SD) to 10 weeks [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): 55.93 (22.43)<br>Week 10 (n=NR): 53.83 (17.72)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **eGFR (ml/min/1.73m$^2$), mean (SD) to 6 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): 55.93 (22.43)<br>Month 6 (n=NR): 61.27 (15.47)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **eGFR (ml/min/1.73m$^2$), mean (SD) to 9 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): 55.93 (22.43)<br>Month 9 (n=NR): 61.71 (23.43)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **eGFR (ml/min/1.73m$^2$), mean (SD) to 12 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): 55.93 (22.43)<br>Month 12 (n=NR): 60.92 (25.63)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **eGFR (ml/min/1.73m$^2$), median (range) to 12 months** | | | | | | | | | |
| 1 prospective cohort study | Very serious limitations[1] | Very serious indirectness[2] | Not applicable | Not calculable | 17 | None | Baseline: 61.5 (7.9 to 132.2) | Critical | VERY LOW |

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|---|---|---|---|---|---|---|---|---|---|
| Gaillard et al 2021 | | | | | | | The authors stated that *"GFR remained stable over the year in our cohort of patients"*; no further details were reported | | |
| **eGFR (mL/min/1.73m$^2$), mean (SD) to 18 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | NR | None | Baseline (n=15): 55.93 (22.43)<br>Month 18 (n=NR): 67.20 (31.17)<br><br>Statistical measures were not reported | Critical | VERY LOW |
| **eGFR (mL/min/1.73m$^2$), mean (SD) and change from baseline to study exit (timeframe not clear)[b] [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 14 | None | Baseline (n=15): 55.93 (22.43)<br>Study exit (n=14): 63.79 (21.44)<br><br>*Mean (SD) change from baseline to study exit: 8.14 (15.48 ml/min/1.73m$^2$); no statistical measures were reported* | Critical | VERY LOW |
| **eGFR (mL/min/1.73m$^2$), mean (SD) to 24 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[6] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | Baseline: 63 (25)<br>At 24 months: 57 (25)<br><br>*Mean change from baseline: p=0.32* | Critical | VERY LOW |
| **Number of patients needing renal transplant, n to 24 months** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Very serious limitations[7] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | 1 patient underwent renal transplant at 17 months | Critical | VERY LOW |
| **Number of patients needing renal replacement therapy (dialysis), n to 24 months** | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Very serious limitations[7] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | 1 patient withdrew from the study at 21 months due to a decline in eGFR and the need for maintenance dialysis | Critical | VERY LOW |
| **Quality of life (1 prospective single-arm follow-up study)** | | | | | | | | | |
| **Percentage change in PedsQL,[e] slope (LSM; SEM not reported)[f] to 24 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[6] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | Physical: 0.302; *change from baseline (p=0.054)*<br>Emotional: 0.019; *change from baseline (p=0.890)*<br>Social: 0.492; *change from baseline (p=0.201)*<br>School: 0.126; *change from baseline (p=0.598)*<br><br>Total: 0.184; *change from baseline (p=0.072)* | Important | VERY LOW |
| **Growth measurements (1 prospective single-arm follow-up study, 1 prospective case series)** | | | | | | | | | |
| **Z-score (height), mean (SD) to week 2 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -3.2 (1.6)<br>Week 2 (n=NR): -2.9 (1.5)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (height), mean (SD) to week 12 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -3.2 (1.6)<br>Week 12 (n=NR): -2.5 (1.5)<br><br>Statistical measures were not reported | Important | VERY LOW |

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|---|---|---|---|---|---|---|---|---|---|
| **Z-score (height), mean (SD) to month 6 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -3.2 (1.6)<br>Month 6 (n=NR): -2.0 (1.7)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (height), mean (SD) to month 12 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -3.2 (1.6)<br>Month 12 (n=NR): -1.1 (1.9)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (height), mean (SD) to month 18 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -3.2 (1.6)<br>Month 18 (n=NR): 0.1 (2.1)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (height), mean (SD) to study exit (timeframe not clear)[b] [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -3.2 (1.6)<br>Study exit (n=15): 0.1 (2.0)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (weight), mean (SD) to week 2 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -4.0 (2.1)<br>Week 2 (n=NR): -3.9 (2.1)<br><br>Statistical measures were not reported | Important | VERY LOW |

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|---|---|---|---|---|---|---|---|---|---|
| **Z-score (weight), mean (SD) to week 12 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -4.0 (2.1)<br>Week 12 (n=NR): -3.3 (2.1)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (weight), mean (SD) to month 6 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -4.0 (2.1)<br>Month 6 (n=NR): -2.8 (2.3)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (weight), mean (SD) to month 12 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -4.0 (2.1)<br>Month 12 (n=NR): -2.2 (1.7)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (weight), mean (SD) to month 18 [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -4.0 (2.1)<br>Month 18 (n=NR): -1.3 (2.0)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (weight), mean (SD) to study exit (timeframe not clear)[b] [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -4.0 (2.1)<br>Study exit (n=15): -1.1 (1.8)<br><br>Statistical measures were not reported | Important | VERY LOW |

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| **Z-score (BSA), mean (SD) to study exit (timeframe not clear)[b] [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -1.8 (1.1)<br>Study exit (n=14): -1.3 (1.1)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (BMI), mean (SD) to study exit (timeframe not clear)[b] [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Very serious limitations[5] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | Baseline (n=15): -1.0 (1.1)<br>Study exit (n=14): -1.2 (1.3)<br><br>Statistical measures were not reported | Important | VERY LOW |
| **Z-score (height),[g] mean (SD) to 24 months [higher values indicate improvement and positive values indicate benefit]** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[6] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | Baseline: -1.15 (-0.93)<br>Month 24: -1.21 (-0.96)<br><br>*Mean change from baseline: p=0.46* | Important | VERY LOW |
| **BMI (kg/m$^2$), mean (SD) to 24 months [higher values indicate benefit]** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[6] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | Baseline: 18.2 (3.1)<br>Month 24: 18.3 (3.2)<br><br>*Mean change from baseline: p=0.27* | Important | VERY LOW |
| **Safety (1 prospective single-arm follow-up study, 1 prospective case series)** | | | | | | | | | |
| **Number of patients experiencing any AE, n (%) at study exit (timeframe not clear)[b]** | | | | | | | | | |
| 1 prospective case series | Serious limitations[3] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | 15 (100); it was unclear whether the AEs were treatment-related | Important | VERY LOW |

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|---|---|---|---|---|---|---|---|---|---|
| Vaisbich et al 2022 | | | | | | | | | |
| **Number of patients experiencing at least 1 AE, n (%) at 24 months** | | | | | | | | | |
| 1 prospective single-arm follow-up study<br><br>Langman et al 2014 | Serious limitations[6] | Serious indirectness[4] | Not applicable | Not calculable | 40 | None | 40 (100); all AEs were treatment-related (35 [87.5%] patients experienced gastrointestinal disorders[h]) | Important | VERY LOW |
| **Number of patients experiencing at least 1 SAEs, n (%) at study exit (timeframe not clear)[b]** | | | | | | | | | |
| 1 prospective case series<br><br>Vaisbich et al 2022 | Serious limitations[3] | Serious indirectness[4] | Not applicable | Not calculable | 15 | None | 12 (80.0) [for a total of 36 SAEs]; none of the SAEs were considered to be treatment-related:<br><br>*Gastroenteritis: 5/15 (33.3)*<br>*Dehydration: 4/15 (26.7)*<br>*Vomiting: 4/15 (26.7)*<br>*Electrolyte imbalance: 2/15 (13.3)*<br>*Gastrostomy: 2/15 (13.3)*<br>*"One patient died on Day 17 of study treatment, during the titration period, the patient had four grade 5 SAEs: gastroenteritis, hypovolemic shock, cardiopulmonary failure, and Fanconi syndrome. The patient was hospitalised and died the next day. In the Investigator's assessment, the SAEs were likely related to the underlying cystinosis and not related to the study treatment"* | Important | VERY LOW |

**Abbreviations**

AE: adverse event; DR: delayed-release; eGFR: estimated glomerular filtration rate; LSM: least squares mean; m: metre; mg: milligram; min: minute; ml: millilitre; nmol; nanomole; NR: not reported; PedsQL: paediatric quality of life inventory; SAE: serious adverse event; SD: standard deviation; SEM: standard error of the mean; WBC: white blood cell.

*1 Risk of bias: very serious limitations due to unclear confounding, and lack of statistical analyses.*

*2 Indirectness: very serious indirectness due to lack of comparator group and outcomes reported for all patients (including 4 patients who switched from SA to DR cysteamine).*
*3 Risk of bias: serious limitations due to non-consecutive and incomplete inclusion of participants.*
*4 Indirectness: serious indirectness due to lack of comparator group.*
*5 Risk of bias: very serious limitations due to non-consecutive and incomplete inclusion of participants and lack of statistical analyses.*
*6 Risk of bias: serious limitations due to incomplete inclusion of participants.*
*7 Risk of bias: very serious limitations due to incomplete inclusion of participants, and lack of statistical analyses.*
*8 Risk of bias: very serious limitations due to unclear confounding and use of subjective measures.*

a Individual percentage of visits with leukocyte cystine levels ≤1 nmol hemicystine/mg protein. WBC <1 nmol hemicystine/mg protein is considered optimal.
b Study exit timeframe was not defined. Treatment duration ranged from 0.5 months [1 patient received only 1 dose of DR cysteamine] and 21 months. The study authors stated that 14 patients completed the study with at least 12 months of treatment and 10 patients completed at least 18 months of treatment.
c The PICO document states that the target white cell cystine content is less than 1 nmol hemicystine/mg protein, and this is considered optimal.
d Participants evaluated their adherence answering the following question on a visual analogical scale: *"How do you evaluate your adherence to cysteamine?"* at each study visit; no further details were provided, but for we have assumed this was measured using a score of 1 to 10. Individual average of self-reported adherence over the year.
e PedsQL is a paediatric quality of life questionnaire assessing four areas of functionality: physical, emotional, social, and school. Details on the PedsQL scoring algorithm were not reported, but higher values indicate better health related quality of life.
f The slope represents the change from baseline to 24 months follow-up in the 2-year follow-up to the crossover RCT during treatment with DR cysteamine.
g The authors stated that *"No patient using growth hormone during the study were evaluated for growth change with the other members of the study"*, but no further details were reported.
h In terms of specific symptoms, emesis was experienced by 28 (70.0%) participants, followed by headache in 14 (35.0%) participants, upper respiratory tract symptoms in 9 (22.5%) participants, and diarrhoea in 8 (20.0%) participants.

# Glossary

| Term | Definition |
|---|---|
| Adverse event | Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention. |
| Baseline | The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared. |
| Bias | Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted. |
| Blinding | A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. |
| Case series | Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients. |
| Clinical importance | A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals. |
| Comparative cohort study | An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. |
| Comparator | The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care). |
| Confidence interval (CI) | A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied).<br>The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. |
| Crossover study design | A study comparing two or more treatments. Once people in the study have completed a course of one treatment they are switched to a different treatment. |
| GRADE (Grading of recommendations assessment, development and evaluation) | A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group. |

| Term | Definition |
|---|---|
| Intention-to-treat analysis (ITT) | An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least one dose of a study drug. |
| Minimal clinically important difference | The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment. |
| Objective measure | A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study. |
| Per-protocol analysis (PP) | A comparison of treatment groups in a trial that includes only those patients who completed the treatment they were originally allocated to. If done alone, this analysis leads to bias. |
| PICO (population, intervention, comparison and outcome) framework | A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been). |
| Prospective study | A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies. |
| P-value (p) | The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be. |
| Randomised controlled trial (RCT) | A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias. |
| Retrospective study | A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected. |

| Term | Definition |
|---|---|
| Single-arm trial | A clinical trial in which all participants receive the experimental intervention of interest. This is especially common in phase I and II trials. |
| Standard deviation (SD) | A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data. |
| Statistical power | The ability of a study to demonstrate an association or causal relationship between two variables (if an association exists) means that the study is statistically significant. The statistical power of a study is primarily related to the number of people included. If too few people are included, any differences in the outcomes will not be statistically significant. |
| Statistical significance | A statistically significant result is one that is assessed as being due to a true effect rather than random chance. |
| Subgroup analysis | A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set. |

# References

## Included studies


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