**Additional file 1:**

**Supplementary table 1. Search syntax used in different databases to gather the bibliographic data.**

|  |
| --- |
| **1. Pubmed:** |
| (("Mucopolysaccharidosis"[All Fields] AND "II"[All Fields]) OR "Mucopolysaccharidosis II"[All Fields] OR "MPS II"[All Fields] OR "Hunter syndrome"[All Fields]) AND ("idursulfase"[All Fields] OR "enzyme replacement therapy"[All Fields] OR "ert"[All Fields]) OR "iduronate-2-sulphatase"[All Fields] AND ("case reports"[Publication Type] OR "case"[All Fields] OR "report"[All Fields]) |
|  |
| **2. Embase:** |
| 'hunter syndrome' AND ('enzyme replacement' OR 'iduronate 2 sulfatase' OR 'idursulfase') AND ('case report' OR 'case study' OR 'medical record review') |
|  |
| **3. Cochrane:** |
| (“Mucopolysaccharidosis II” OR "Hunter syndrome") AND (“enzyme replacement” OR idursulfase OR “iduronate-2-sulphatase”) |
|  |
| **4. LYLACS (webpage: http://lilacs.bvsalud.org/es/):** |
| (Title, Summary, Issue) |
| “mucopolysaccharidosis II” and “'enzyme replacement” |

**Supplementary table 2. Case reports of males with MPS-II published prior to the bibliographic search of meta-analysis of clinical studies (January 2008 to December 2015).**

| **Reference**  **Publication**  **Included in Bradley study.** | **(Severe or attenuated)**  **Mutations** | **Age at diagnosis**  **Age at ERT start**  **ERT duration** | **Treatment**  **IV Dose**  **Schedule** | **Outcomes evaluated in Bradley meta-analysis modified (improved or impaired (IRR)) after ERT**  **(Novelties)** |
| --- | --- | --- | --- | --- |
| **Studies published prior to the bibliographic search of the meta-analysis of clinical studies (2008 to December 2015)** | | | | |
| **Kim et al, 2014 1**  Journal article  Not included | (S)  ? | 72 months  72 months  15 months | Idursulfase  0.5 to 1  mg/kg/weekly | **uGAGs; LiverV**; 6MWT or endurance; pulmonary function; **antibodies**.  (Immune modulation protocol) |
| **NoH et al, 2014 2**  Letter to editor  Not included | (?)  ? | 72 months  72 months  4 months | Idursulfase  0.5  mg/kg/weekly | (Skin lesions decrease after ERT) |
| **Lampe et al, 2014 3**  Journal article  1 MPS-II  *Included* | (?)  p.R88H mutation | Pre-natal  0.3 months  2.3 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs.**  (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  1 MPS-II  *Included* | (?)  p.R95G mutation | 1 week  1.4 months  22.6 months | Idursulfase  1.5 to 0.5  mg/kg/weekly | **LiverV**  (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  1 MPS-II  *Included* | (?)  p.P86L mutation | 6 weeks  2 months  2.3 months | Idursulfase  0.6 to 0.5  mg/kg/weekly | **uGAGs.**  (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  *Included* | (?)  p.R493P mutation | 1 day  2.3 months  36 months | Idursulfase  0.6 to 0.5  mg/kg/weekly | **uGAGs;** LiverV; 6MWT or endurance; Growth  (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  *Included* | (?)  c.1270insCC | 4 weeks  2.5 months  5 years | Idursulfase  0.5  mg/kg/weekly | **uGAGs;** LiverV.  (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  *Included* | (?)  p.G336E | 11 weeks  2.8 months  17 months | Idursulfase  0.5  mg/kg/weekly | **LiverV.**  (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  *Included* | (?)  c.1133A>G | 1 week  6 months  4 years | Idursulfase  0.5  mg/kg/weekly | (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**  Journal article  *Included* | (?)  c.1362-1365dup | 5.5 months  6.5 months  4 years | Idursulfase  0.66 to 0.5  mg/kg/weekly | **uGAGs;** LiverV.  (Safety and efficacy evaluation of ERT) |
| **Christianto et al, 2013 4**  Journal article  Not included | (S)  c.1053delT in exon 8 | 6 years  27 years  12 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs; LiverV**; 6MWT or endurance; **antibodies**.  (Safety and efficacy evaluation of ERT) |
| **Volpi et al, 2013 5**  Journal article  Not included | (S)  P120R mutation on Xq28 | 2 years and 9 m.  3 years  10 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs**  (Study of plasmatic  dermatan sulfate (DS) during ERT) |
| **Sato et al, 2013 6**  Journal article  Not included | (S)  ? | 3 years  7 years  24 months | Idursulfase  0.5  mg/kg/weekly | (Limited efficacy for  cardiac valve disease of ERT) |
| **Tajima et al, 2013 7**  Journal article  *Included* | (S)  Recombination IDS gene and the IDS-2 pseudogene | 3 years  3 years  34 months | Idursulfase  0.3 - 0.5  mg/kg/weekly | **uGAGs; LiverV**  (Safety and efficacy evaluation of ERT) |
| **Tajima et al, 2013 7**  Journal article  *Included* | (S)  Recombination IDS gene and the IDS-2 pseudogene | 4 months  4 months  32 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs;**  (Safety and efficacy evaluation of pre-symptomatic initiation of ERT) |
| **Puiu M et al, 2013 8**  Journal article  Not included | (S)  ? | 3 years  3 years and 3 m.  1 year | Idursulfase  0.5  mg/kg/weekly | **LiverV**; 6MWT; JROM; Growth; QoL; Sleep apnea.  (Improvement of cognitive and conductual functioning after ERT) |
| **Marín LL et al, 2012 9**  Short report  Not included | (A)  ? | 6 years  9 years  9 months | Idursulfase  0.5  mg/kg/weekly | (Improvement of skin lesion after ERT) |
| **Hoffmann B et al, 2011 10**  Journal article  Not included | (A)  A85T, missense mutation | 8 years  ?  20 months | Idursulfase  0.5  mg/kg/weekly | LiverV; 6MWT or endurance; **Growth;** QoL;  (Safety and efficacy evaluation of ERT) |
| **Hoffmann B et al, 2011 10**  Journal article  Not included | (S)  missense  mutation C184F | 5 years  ?  22 months | Idursulfase  0.5  mg/kg/weekly | LiverV; 6MWT or endurance; **Growth;** QoL;  (Safety and efficacy evaluation of ERT) |
| **Hoffmann B et al, 2011 10**  Journal article  Not included | (S)  131del10, frame-shift mutation | 5 years  ?  31 months | Idursulfase  0.5  mg/kg/weekly | 6MWT or endurance; **Growth;** QoL;  (Safety and efficacy evaluation of ERT) |
| **Tylki-Szymanska et al, 2012 11**  Journal article  *Included* | (¿)  missense mutationc.1568A>G in exon 9 of the IDS gene | 3 months  3 months  36 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs;**  (Safety and efficacy evaluation of ERT) |
| **Papadia F et al, 2011 12**  Journal article  Not included | (S)  Splice site mutation(c.418+1  G>C). | 3 years  4 years ant 10 m. 3 years | Idursulfase  0.5  mg/kg/weekly | **uGAGs;** **LiverV; JROM**;  (Early use of ERT improve bone abnormalities) |
| **Pérez-Calvo et al, 2011**13  Journal article  Not included | (A)  un genotipo R443/X | 18 months  30 years  6 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs; 6MWT; JROM**; QoL; **antibodies**.  (The JROM in later stages of disease may benefit from ERT) |
| **Tchan MC et al, 2011** 14  Journal article  Not included | (A)  ? | 20 years  44 years  12 months | Idursulfase  30  mg/weekly | **uGAGs; 6MWT;** QoL.  (Safety and efficacy evaluation of ERT in adult age) |
| **Tchan MC et al, 2011** 14  Journal article  Not included | (A)  ? | 26 years  51 years  12 months | Idursulfase  36  mg/weekly | **uGAGs; 6MWT**; QoL.  (Safety and efficacy evaluation of ERT in adult age) |
| **Tchan MC et al, 2011** 14  Journal article  Not included | (A)  ? | 22 years  46 years  12 months | Idursulfase  36  mg/weekly | **uGAGs;** QoL; **IRR.**  (Safety and efficacy evaluation of ERT in adult age) |
| **Wang RY et al, 2009**  15  Journal article  Not included | (A)  homozygous P533R IDUA mutations | 3 years and 9 m.  3 years and 11 m.  2 years and 6 m. | Idursulfase  0.5  mg/kg/weekly | **uGAGs;**  (Evaluate central nervous system effects in MPS II patients) |
| **Wang RY et al, 2009**  **15**  Journal article  Not included | (A)  IDS mutation, hemizygous R8X mutation | 4 years and 7 m.  4 years and 11 m.  ? | Idursulfase  0.5  mg/kg/weekly | **uGAGs;**  (Evaluate central nervous system effects in MPS II patients) |
| **Galán Gómez E et al, 2008 16**  Letter to editor  Not included | (S)  I2S gene showed an N350H  mutation in exon 8 | 7 months  3 years  27 weeks | Idursulfase  0.5  mg/kg/weekly | **uGAGs; Liver;** 6MWT; **antibodies**.  (The JROM in later stages of disease may benefit from ERT) |
| **Westhoff M et al, 2011 17**  Journal article  Not included | (A)  ? | 3 years  37 years  24 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs; 6MWT; JROM; pulmonary function;**  (ERT benefits adult Hunter patients in restrictive ventilatory defects.) |
| **Sanchez JI et al, 2015 18**  Congress  Not included | ?  ? | ?  ?  ? | Idursulfase  ?  ? | (ERT improve macular edema in MPS-II patient.) |
| **Gkavogiannakis N et al, 2015 19**  Congress  1 MPS-II  Males | (A)  ? | 34 years  ?  ? | Idursulfase  ?  ? | **IRR; antibodies.**  (Successful desensitization procedure to idursulfase.) |
| **Fischer et al, 2015 20**  Congress  Not included | ?  ? | ?  4 years  ? | Idursulfase  ?  ? | (Idursulfase did not precipitate/worsen autoimmune anemia or thrombocytopenia) |
| **Lau HA et al, 2015 21**  Congress  Not included | (A)  ? | ?  35 years  21 months | Idursulfase  ?  ? | (ERT did not prevent progression of vision loss) |
| **Kinoshita M et al, 2014 22**  Congress  Not included | (A)  ? | 5 years  20 years  ? | Idursulfase  ?  ? | (ERT improves cortical function but aggravated epileptogenic.) |
| **Bivina L et al, 2014 23**  Congress  Not included | ?  ? | 6 years  6 years  4 years | Idursulfase  ?  ? | (Early ERT and transplant slowed progression of the disease) |
| **Bivina L et al, 2014**  **23**  Congress  Not included | ?  ? | 2.5 years  2.5 years  8.5 years | Idursulfase  ?  ? | (Early ERT and transplant slowed progression of the disease) |
| **Bivina L et al, 2014**  **23**  Congress  Not included | ?  ? | Pre-nataly  4 months  ? | Idursulfase  ?  ? | Growth; developmental improvements  (Early ERT and transplant slowed progression of the disease) |
| **Nava E et al, 2012 24**  Journal article  Not included | (S)  complete exon 7 deletion in the iduronate 2-sulfatase gene | 2 years and 4 m.  4 years and 9 m.  2 years and 1 m. | Idursulfase  ?  ? | 6MWT; **JROM;**  (Botulinum Toxin for the  Treatment of Equinus Deformity in MPS-II Patients) |
| **Nava E et al, 2012 24**  Journal article  Not included | (S)  ? | 1 year and 1 m.  6 years and 6 m.  3 years | Idursulfase  ?  ? | (Botulinum Toxin for the  Treatment of Equinus Deformity in MPS-II Patients) |
| **Bonanni P et al, 2012 25**  Journal article  Not included | (S)  ? | 1 year and 7 m.  8 years and 3 m.  14 months | Idursulfase  ?  ? | (Epilepsy may be a treatable cause of neurological regression in  individuals with MPS II) |
| **Uz B et al, 2012 26**  Letter to editor  Not included | (A)  ? | Newborn period  10 years and 2 m.  8 months | Idursulfase  0.5  mg/kg/weekly | (Hunter syndrome and new onset idiopathic thrombocytopenic purpura) |
| **Farooq MU et al, 2008 27**  Letter to editor  Not included | ?  IDS gene, a (A>T) change at nucleotide 595 | 2 year  11 years and 6 m.  12 months | Idursulfase  0.5  mg/kg/weekly | Liver; pulmonary function;  (Novel mutation in the Iduronate 2 sulfatase gene resulting in MPS-II and Chorea.) |
| **Farooq MU et al, 2008**  **27**  Letter to editor  Not included | ?  IDS gene, a (A>T) change at nucleotide 595 | 4 years  13 years  12 months | Idursulfase  0.5  mg/kg/weekly | Liver; pulmonary function;  (Novel mutation in the Iduronate 2 sulfatase gene resulting in MPS-II and Chorea.) |
| *?:No data in the study´s paper; 6MWT: 6-minute walk test; Cardiac (ECHO): Cardiac evaluation with echocardiogram; IRR: infusion-related reaction; IV: Intra-venous; JROM; joint range of motion; MPS-II: Mucopolysaccharidosis type II; QoL: Quality of life; SOE: Strenght of evidence; uGAGs: Urinary glycosaminoglycans.* | | | | |

**Supplementary table 3. Case reports of males with MPS-II published later to the bibliographic search of the meta-analysis of clinical studies (January 2016 to April 2018).**

| **Reference**  **Publication** | **(Severe or attenuated)**  **Mutations** | **Age at diagnosis**  **Age at ERT start**  **ERT duration** | **Treatment**  **IV Dose**  **Schedule** | **Outcomes evaluated in Bradley meta-analysis modified (improved or impaired (IRR)) after ERT**  **(Novelties)** |
| --- | --- | --- | --- | --- |
| **Studies published later to the bibliographic search of the meta-analysis of clinical studies (January 2016 to April 2018).** | | | | |
| **Kim et al, 2017 28**  Journal article | (S)  ? | 14 months  15 months  5 years | Idursulfase  0.5 to 1 mg/kg/weekly | **uGAGs;** 6MWT or endurance; JROM; pulmonary function; **antibodies**.  (uGAGs as biomarker for antibodies;  Anti-immunological scheme) |
| **Ngu et al, 2017 29**  Journal article | (A)  c.1608\_1609delTA (p.Tyr536Ter) mutation  exon 9 IDS gene | 6 years  11 years  20 / 24 months | Idursulfase / idursulfase beta  0.5 / 1.67 to 0.5  mg/kg/weekly | **uGAGs; LiverV**; **6MWT**; growth; **Cardiac (ECHO);** sleep disorder; **antibodies**.  (idursulfase beta after idursulfase as  Anti-immunological scheme) |
| **Nishiyama et al, 2016 30**  Journal article | (A)  ? | 6 years  6 years  18 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs;** LiverV; Spleen Volume; JROM; sleep disorder.  (Hydroneprhosis resolution) |
| **Gupta et al, 2014 31 &**  **Madireddi et al, 2016 32**  Journal article | (A)  mutation A85T  caused by a G to A substitution at nucleotide position c.253 in the exon 3 of IDS | 24 years  24 years  4 months | Idursulfase  0.5  mg/kg/weekly | **Spleen Volume; 6MWT;** JROM; pulmonary function; QoL.  (Diagnosis of MPS-II by enzyme  assay and mutational analysis) |
| **Akiyama R et al, 2018 33**  Congress | (A)  ? | 12 years  12 years  ? months | Enzyme replacement therapy | Growth  (Optic abnormalities not changed by ERT treatment) |
| **Al B et al, 2017 34**  Journal article | (S)  ? | 10 days  10 days  1.4 months | Idursulfase  0.5  mg/kg/weekly | **uGAGs.**  (hematopoietic  stem cell transplantation (HSCT)) |
| **Jarstad A eta al, 2017** 35  Congress | (A)  ? | 35 years  39 years  4 years | Enzyme replacement therapy | (Optic abnormalities not changed by ERT) |
| **Moreno KJ et al, 2017 36**  Congress | (A)  hemizygous mutation in intron 5 of the IDS gene, c.709-658GN A. | 25 years  25 years  6 months | Idursulfase  0.5  mg/kg/weekly | **Cardiac (ECHO)**; QoL.  (Cardiac improvement after ERT) |
| **Bettocchi I et al, 2016 37**  Congress | (S)  IDS gene deletion of exons 1-7, extending to regions Xq28 e Xq27.3, removing the entire pseudogene IDS2 and genes FMR1 and AFF2 | 3 months  18 months  35. years | Idursulfase  0.5  mg/kg/weekly | (MPS-II mutation analysis) |
| **Romero FHC et al, 2016 38**  Congress | (S)  IDS/IDSP1 inversion | 3 years  ? months  3 years | Idursulfase  0.5  mg/kg/weekly | **IRR.**  (Adverse events under Idursulfase treatment) |
| **Romero FHC et al, 2016 38**  Congress | (S)  IDS/IDSP1 inversion | 36 months  ? months  2 years | Idursulfase  0.5  mg/kg/weekly | **IRR.**  (Adverse events under Idursulfase treatment) |
| **Romero FHC et al, 2016 38**  Congress | (S)  IDS/IDSP1 inversion | 3 years  ? months  5 years | Idursulfase  0.5  mg/kg/weekly | **IRR.**  (Adverse events under Idursulfase treatment) |
| *?:No data in the study´s paper; 6MWT: 6-minute walk test; Cardiac (ECHO): Cardiac evaluation with echocardiogram; IRR: infusion-related reaction; IV: Intra-venous; JROM; joint range of motion; MPS-II: Mucopolysaccharidosis type II; QoL: Quality of life; SOE: strenght of evidence; uGAGs: Urinary glycosaminoglycans.* | | | | |

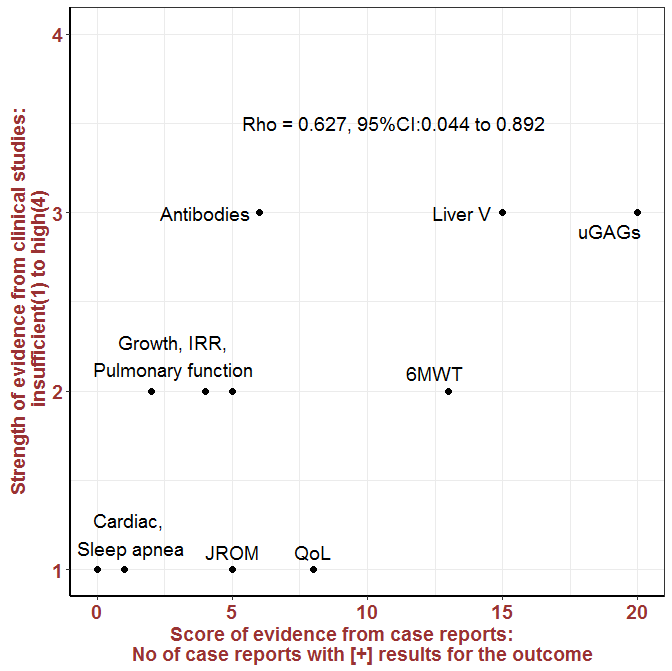
**Supplementary table 4. Agreement between the classification of outcomes based on the case report meta-analysis and the SOE classification based on the clinical study meta-analysis. Weak confirmatory method.**

|  |  |  |
| --- | --- | --- |
|  | **Strength of evidence of clinical study meta-analysis** | |
| **Number of case reports [+] for the outcome** | **High to  moderate** | **Low to  insufficient** |
| **≥ 6 [+] of 44 cases**  **(acceptable evidence group)** | (True positives= 3)  -uGAGs -Liver Volume -Antibodies | (False positive=2)  -6WMT, QoL, |
| **< 6 [+] of 44 cases**  **(unacceptable evidence group)** | (False negative=0) | (True negatives=6) - Growth, JROM, Pulmonary function, IRR, sleep apnea, Cardiac. |

*The 95% confidence interval for the validity index are: positive predictive value: 60% (15 to 95%); negative predictive value: 100% (54 to 100%); sensibility: 100% (29 to 100%) and specificity: 75% (35 to 97%).*

*6MWT: 6-minute walk test; CI: Confidence interval; IRR: Infusion-related reaction; JROM; Joint range of motion; NPV: Negative predictive value; PPV: Positive predictive value; QoL: Quality of life; Se: Sensitivity; Sp: Specificity; SOE: Strenght of evidence; uGAGs: Urinary glycosaminoglycans.*

**Supplementary figure 1. Agreement between the score of evidence from the case report meta-analysis and SOE from the clinical study meta-analysis. Weak confirmatory method.**



*6MWT: 6-minute walk test; CI: Confidence interval; IRR: Infusion-related reaction; JROM: Joint range of motion; QoL: Quality of life; Rho: Spearman correlation coefficient; SOE: Strenght of evidence; uGAGs: Urinary glycosaminoglycans.*

**Supplementary table 5. Sensitivity analysis on different futility boundaries.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Futility boundary\*** | **True (+/-); False (+/-)** | **Accuracy%** | **Se%** | **Sp%** | **PPV%** | **NPV%** |
| 5% \*\* | (3/8); (0/0) | 100 | 100 | 100 | 100 | 100 |
| 1% | (3/5); (3/0) | 73 | 100 | 62 | 50 | 100 |
| 10% | (1/8); (0/2) | 82 | 33 | 100 | 100 | 80 |
| 15% | (1/8); (0/2) | 82 | 33 | 100 | 100 | 80 |
| 20% | (1/8); (0/2) | 82 | 33 | 100 | 100 | 80 |
| 50% | (0/8); (0/3) | 73 | 0 | 100 | 0 | 73 |

*\*The analyses were done in primary analysis set: All case reports of males MPS-II treated with ERT that report efficacy and safety. This case reports were written in a narrative form (results not aggregated) and published prior to Bradley bibliographic search.*

*\*\* The futility boundary has been considered the null hypothesis of the analysis.*

*6MWT: 6-minute walk test; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; Rho: Spearman correlation coefficient; Se: Sensitivity; Sp: Specificity.*

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