**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 articleNot included | (S)? | 72 months72 months15 months | Idursulfase0.5 to 1mg/kg/weekly | **uGAGs; LiverV**; 6MWT or endurance; pulmonary function; **antibodies**.(Immune modulation protocol) |
| **NoH et al, 2014 2**Letter to editorNot included | (?)? | 72 months72 months4 months | Idursulfase0.5mg/kg/weekly | (Skin lesions decrease after ERT) |
| **Lampe et al, 2014 3**Journal article1 MPS-II*Included* | (?)p.R88H mutation | Pre-natal0.3 months2.3 months | Idursulfase0.5mg/kg/weekly | **uGAGs.**(Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**Journal article1 MPS-II*Included* | (?)p.R95G mutation | 1 week1.4 months22.6 months | Idursulfase1.5 to 0.5mg/kg/weekly | **LiverV**(Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**Journal article1 MPS-II*Included* | (?)p.P86L mutation | 6 weeks2 months2.3 months | Idursulfase0.6 to 0.5mg/kg/weekly | **uGAGs.**(Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**Journal article*Included* | (?)p.R493P mutation | 1 day2.3 months36 months | Idursulfase0.6 to 0.5mg/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 weeks2.5 months5 years | Idursulfase0.5mg/kg/weekly  | **uGAGs;** LiverV.(Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**Journal article*Included* | (?)p.G336E | 11 weeks2.8 months17 months | Idursulfase0.5mg/kg/weekly | **LiverV.**(Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**Journal article*Included* | (?)c.1133A>G | 1 week6 months4 years | Idursulfase0.5mg/kg/weekly | (Safety and efficacy evaluation of ERT) |
| **Lampe et al, 2014 3**Journal article*Included*  | (?)c.1362-1365dup | 5.5 months6.5 months4 years | Idursulfase0.66 to 0.5mg/kg/weekly | **uGAGs;** LiverV.(Safety and efficacy evaluation of ERT) |
| **Christianto et al, 2013 4**Journal articleNot included | (S)c.1053delT in exon 8 | 6 years27 years12 months | Idursulfase0.5mg/kg/weekly | **uGAGs; LiverV**; 6MWT or endurance; **antibodies**.(Safety and efficacy evaluation of ERT) |
| **Volpi et al, 2013 5**Journal articleNot included | (S)P120R mutation on Xq28 | 2 years and 9 m.3 years10 months | Idursulfase0.5mg/kg/weekly | **uGAGs**(Study of plasmaticdermatan sulfate (DS) during ERT) |
| **Sato et al, 2013 6**Journal articleNot included | (S)? | 3 years7 years24 months | Idursulfase0.5mg/kg/weekly | (Limited efficacy forcardiac valve disease of ERT) |
| **Tajima et al, 2013 7**Journal article*Included* | (S)Recombination IDS gene and the IDS-2 pseudogene | 3 years3 years34 months | Idursulfase0.3 - 0.5mg/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 months4 months32 months | Idursulfase0.5mg/kg/weekly | **uGAGs;** (Safety and efficacy evaluation of pre-symptomatic initiation of ERT) |
| **Puiu M et al, 2013 8**Journal articleNot included | (S)? | 3 years3 years and 3 m. 1 year | Idursulfase0.5mg/kg/weekly | **LiverV**; 6MWT; JROM; Growth; QoL; Sleep apnea.(Improvement of cognitive and conductual functioning after ERT) |
| **Marín LL et al, 2012 9**Short reportNot included | (A)? | 6 years9 years9 months | Idursulfase0.5mg/kg/weekly | (Improvement of skin lesion after ERT) |
| **Hoffmann B et al, 2011 10**Journal articleNot included | (A)A85T, missense mutation | 8 years?20 months | Idursulfase0.5mg/kg/weekly | LiverV; 6MWT or endurance; **Growth;** QoL;(Safety and efficacy evaluation of ERT) |
| **Hoffmann B et al, 2011 10**Journal articleNot included | (S)missensemutation C184F | 5 years?22 months | Idursulfase0.5mg/kg/weekly | LiverV; 6MWT or endurance; **Growth;** QoL;(Safety and efficacy evaluation of ERT) |
| **Hoffmann B et al, 2011 10**Journal articleNot included | (S)131del10, frame-shift mutation | 5 years?31 months | Idursulfase0.5mg/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 months3 months36 months | Idursulfase0.5mg/kg/weekly | **uGAGs;**(Safety and efficacy evaluation of ERT) |
| **Papadia F et al, 2011 12**Journal articleNot included | (S)Splice site mutation(c.418+1G>C). | 3 years4 years ant 10 m. 3 years | Idursulfase0.5mg/kg/weekly | **uGAGs;** **LiverV; JROM**;(Early use of ERT improve bone abnormalities) |
| **Pérez-Calvo et al, 2011**13 Journal articleNot included | (A)un genotipo R443/X | 18 months30 years6 months | Idursulfase0.5mg/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 articleNot included | (A)? | 20 years44 years 12 months | Idursulfase30mg/weekly | **uGAGs; 6MWT;** QoL.(Safety and efficacy evaluation of ERT in adult age) |
| **Tchan MC et al, 2011** 14Journal articleNot included | (A)? | 26 years51 years12 months | Idursulfase36mg/weekly | **uGAGs; 6MWT**; QoL.(Safety and efficacy evaluation of ERT in adult age) |
| **Tchan MC et al, 2011** 14Journal articleNot included | (A)? | 22 years46 years12 months | Idursulfase36mg/weekly | **uGAGs;** QoL; **IRR.**(Safety and efficacy evaluation of ERT in adult age) |
| **Wang RY et al, 2009** 15Journal articleNot included | (A)homozygous P533R IDUA mutations | 3 years and 9 m.3 years and 11 m.2 years and 6 m. | Idursulfase0.5mg/kg/weekly | **uGAGs;**(Evaluate central nervous system effects in MPS II patients) |
| **Wang RY et al, 2009** **15**Journal articleNot included | (A)IDS mutation, hemizygous R8X mutation | 4 years and 7 m.4 years and 11 m.? | Idursulfase0.5mg/kg/weekly | **uGAGs;**(Evaluate central nervous system effects in MPS II patients) |
| **Galán Gómez E et al, 2008 16**Letter to editorNot included | (S)I2S gene showed an N350Hmutation in exon 8 | 7 months3 years27 weeks | Idursulfase0.5mg/kg/weekly | **uGAGs; Liver;** 6MWT; **antibodies**.(The JROM in later stages of disease may benefit from ERT) |
| **Westhoff M et al, 2011 17**Journal articleNot included | (A)? | 3 years37 years24 months | Idursulfase0.5mg/kg/weekly | **uGAGs; 6MWT; JROM; pulmonary function;** (ERT benefits adult Hunter patients in restrictive ventilatory defects.) |
| **Sanchez JI et al, 2015 18**CongressNot included | ?? | ??? | Idursulfase?? | (ERT improve macular edema in MPS-II patient.) |
| **Gkavogiannakis N et al, 2015 19**Congress1 MPS-IIMales | (A)? | 34 years?? | Idursulfase?? | **IRR; antibodies.**(Successful desensitization procedure to idursulfase.) |
| **Fischer et al, 2015 20**CongressNot included | ?? | ?4 years? | Idursulfase?? | (Idursulfase did not precipitate/worsen autoimmune anemia or thrombocytopenia) |
| **Lau HA et al, 2015 21**CongressNot included | (A)? | ?35 years21 months | Idursulfase?? | (ERT did not prevent progression of vision loss) |
| **Kinoshita M et al, 2014 22**CongressNot included | (A)? | 5 years20 years? | Idursulfase?? | (ERT improves cortical function but aggravated epileptogenic.) |
| **Bivina L et al, 2014 23**CongressNot included | ?? | 6 years6 years4 years | Idursulfase?? | (Early ERT and transplant slowed progression of the disease) |
| **Bivina L et al, 2014****23**CongressNot included | ?? | 2.5 years2.5 years8.5 years | Idursulfase?? | (Early ERT and transplant slowed progression of the disease) |
| **Bivina L et al, 2014****23**CongressNot included | ?? | Pre-nataly4 months? | Idursulfase?? | Growth; developmental improvements(Early ERT and transplant slowed progression of the disease) |
| **Nava E et al, 2012 24**Journal articleNot 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 theTreatment of Equinus Deformity in MPS-II Patients) |
| **Nava E et al, 2012 24**Journal articleNot included | (S)? | 1 year and 1 m.6 years and 6 m.3 years | Idursulfase?? | (Botulinum Toxin for theTreatment of Equinus Deformity in MPS-II Patients) |
| **Bonanni P et al, 2012 25**Journal articleNot included | (S)? | 1 year and 7 m.8 years and 3 m.14 months | Idursulfase?? | (Epilepsy may be a treatable cause of neurological regression inindividuals with MPS II) |
| **Uz B et al, 2012 26**Letter to editorNot included | (A)? | Newborn period10 years and 2 m.8 months | Idursulfase0.5mg/kg/weekly | (Hunter syndrome and new onset idiopathic thrombocytopenic purpura) |
| **Farooq MU et al, 2008 27**Letter to editorNot included | ?IDS gene, a (A>T) change at nucleotide 595 | 2 year11 years and 6 m.12 months | Idursulfase0.5mg/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 editorNot included | ?IDS gene, a (A>T) change at nucleotide 595 | 4 years13 years12 months | Idursulfase0.5mg/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 months15 months5 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) mutationexon 9 IDS gene | 6 years11 years20 / 24 months | Idursulfase / idursulfase beta0.5 / 1.67 to 0.5mg/kg/weekly | **uGAGs; LiverV**; **6MWT**; growth; **Cardiac (ECHO);** sleep disorder; **antibodies**.(idursulfase beta after idursulfase asAnti-immunological scheme) |
| **Nishiyama et al, 2016 30**Journal article | (A)? | 6 years6 years18 months | Idursulfase0.5mg/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 years24 years4 months | Idursulfase0.5mg/kg/weekly | **Spleen Volume; 6MWT;** JROM; pulmonary function; QoL.(Diagnosis of MPS-II by enzymeassay and mutational analysis) |
| **Akiyama R et al, 2018 33**Congress | (A)? | 12 years12 years? months | Enzyme replacement therapy | Growth(Optic abnormalities not changed by ERT treatment) |
| **Al B et al, 2017 34**Journal article | (S)? | 10 days10 days1.4 months | Idursulfase0.5mg/kg/weekly | **uGAGs.**(hematopoieticstem cell transplantation (HSCT)) |
| **Jarstad A eta al, 2017** 35Congress | (A)? | 35 years39 years4 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 years25 years6 months | Idursulfase0.5mg/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 months18 months35. years | Idursulfase0.5mg/kg/weekly | (MPS-II mutation analysis) |
| **Romero FHC et al, 2016 38**Congress | (S)IDS/IDSP1 inversion | 3 years? months3 years | Idursulfase0.5mg/kg/weekly | **IRR.**(Adverse events under Idursulfase treatment) |
| **Romero FHC et al, 2016 38**Congress | (S)IDS/IDSP1 inversion | 36 months? months2 years | Idursulfase0.5mg/kg/weekly | **IRR.**(Adverse events under Idursulfase treatment) |
| **Romero FHC et al, 2016 38**Congress | (S)IDS/IDSP1 inversion | 3 years? months5 years | Idursulfase0.5mg/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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