

**NIHR Innovation Observatory  
Evidence Briefing: February 2018****Emapalumab for primary haemophagocytic  
lymphohistiocytosis**

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**LAY SUMMARY**

Haemophagocytic lymphohistiocytosis (HLH) is a severe immune system disorder characterized by over-stimulation of some cells of the immune system. Primary HLH, more common in children, results from genetic abnormalities that leads to malfunction of certain white blood cells, causing the immune system to generate an excessive amount of a chemical substance called interferon gamma (IFN $\gamma$ ). Increased activity of IFN $\gamma$  leads to severe tissue damage and multi-organ failure. HLH is a very rare disease with a high mortality rate with a median survival time that ranges from less than 2 months to 6 months after diagnosis if untreated. Even with treatment, only 55-65% of the patients are expected to survive upto 5 years.

Emapalumab is a type of drug called a monoclonal antibody, under development for the treatment of primary HLH in children. It acts by neutralising IFN $\gamma$  activity produced by over-stimulated cells of the immune system. It is administered as an intravenous infusion and may be used in addition to current treatment. If licensed, emapalumab will be a targeted therapy for patients with primary HLH and has the potential to increase the length of survival.

*This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Primary haemophagocytic lymphohistiocytosis (HLH) (paediatric patients)

## TECHNOLOGY

### DESCRIPTION

Emapalumab (NI-0501) is a human monoclonal antibody that targets interferon gamma (IFN $\gamma$ ).<sup>1</sup> IFN $\gamma$  is a cytokine secreted by cells of the immune system to help regulate immune functions. It is produced by natural killer (NK) and natural killer T-cells (NKT), as well as by CD4+ (immune cells with glycoprotein, cluster of differentiation 4), helper T-cells and CD8+ (immune cells with a glycoprotein, cluster of differentiation 8) and cytotoxic T-lymphocytes in response to specific pathogens. This particular cytokine is important to the immune system, as it directly inhibits the ability of certain viruses and bacteria to replicate and it also helps to both stimulate as well as regulate other immune responses in the body, particularly inflammation.<sup>2</sup> High levels of IFN $\gamma$  lead to macrophage activation and an overproduction of proinflammatory cytokines, which can cause severe tissue damage and organ failure.<sup>3</sup> Emapalumab inhibits the interaction of IFN $\gamma$  with its cognate receptor on T-cells, thereby neutralising IFN $\gamma$  activity.<sup>4</sup>

In the phase III clinical trial to assess the efficacy and safety of emapalumab in primary haemophagocytic lymphohistiocytosis (NCT03312751)<sup>5</sup>, emapalumab will be administered by intravenous infusion, once every 3 days for the first 2 weeks and then twice weekly for 8-12 weeks.<sup>6</sup>

Emapalumab does not currently have Marketing Authorisation in the EU for any indication. It is currently in phase II trials for HLH in patients with systemic juvenile idiopathic arthritis (SJIA).<sup>4</sup>

## INNOVATION and/or ADVANTAGES

Emapalumab is a targeted therapy for this indication.<sup>6</sup> If licensed it will offer an additional treatment option for patients with primary haemophagocytic lymphohistiocytosis.

## DEVELOPER

NovImmune SA

## REGULATORY INFORMATION/ MARKETING PLANS

Emapalumab has been given the following designations for primary haemophagocytic lymphohistiocytosis (HLH):<sup>2</sup>

- orphan drug in the EU and USA in 2010
- PRIME status by the EMA in 2016
- Breakthrough therapy in the USA in 2016

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<sup>a</sup> Information provided by company

## PATIENT GROUP

### BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by excessive activation of macrophages and T-cells<sup>7</sup> due to an over stimulation of the immune system.<sup>8</sup> It is categorized into two different conditions that may be difficult to distinguish from one another: a primary and a secondary form.<sup>9</sup>

Primary HLH is the genetic form of the disease, compared to secondary HLH which is acquired. Primary HLH, an autosomal recessive condition, typically manifests in children with documented genetic abnormalities of the cytotoxic function of natural killer (NK) cells and T-cells.<sup>10</sup> It is diagnosed if there is more than one affected child in the family and/or a gene defect is identified. Several specific gene mutations have been identified but not all patients with primary HLH have a recognised genetic mutation.<sup>11</sup>

The salient features of this disease are systemic release of proinflammatory cytokines, persistent activation of macrophages/histiocytes and T-cells and multi-system inflammation with characteristic clinical and laboratory features of fever, hepatosplenomegaly, cytopenias, coagulopathy and hypertriglyceridaemia.<sup>12</sup>

The disease is seen in all ages and has no predilection for race or sex. The early institution of therapy is critical to control the hypercytokinemia that otherwise will lead to end-organ failure and death.<sup>10</sup>

### CLINICAL NEED and BURDEN OF DISEASE

HLH is a very rare disease with an estimated 1.2 per million children affected by HLH each year. This may be an underestimation as the diagnosis may be missed in some patients. Most affected children (70-80%) become unwell in the first year of life with infection-like symptoms, often triggered by a viral infection. A small number (10%) develop symptoms within the first 4 weeks of life. In the same family, children with familial HLH usually develop symptoms around the same age.<sup>11</sup>

Both primary and secondary forms of HLH, including cases treated adequately, may have a high mortality rate. The long-term outlook (prognosis) of familial forms without treatment is poor, with a median survival time that ranges from less than 2 months to 6 months after diagnosis. Even with treatment, only 55-65% are expected to survive after 3 years.<sup>13,14</sup> Untreated, approximately 95% of children will die of the disease.<sup>10</sup>

The 2016/2017 Hospital Episodes Statistics (HES) Data recorded 342 admissions and 2,750 FCE bed days due to haemophagocytic lymphohistiocytosis (ICD-10 code: D76.1)<sup>15</sup> which includes both primary and secondary HLH. Of the 342 admissions, 152 were children up to 18 years of age.

Based on current literature, population estimates could not be drawn for England and Wales or the UK.

## PATIENT PATHWAY

## RELEVANT GUIDANCE

## NICE GUIDANCE

No guidance identified

## NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS standard contract paediatric medicine: haematology. E03/S/f.

## OTHER GUIDANCE

- Ramachandran S, Zaidi F, Aggarwal A and Gera R. Recent advances in diagnostic and therapeutic guidelines for primary and secondary hemophagocytic lymphohistiocytosis. *Blood Cells Mol Dis.* 2017.<sup>7</sup>
- Henter J, Horne A, Arico M, Egeler M, Filipovich AH et al. *Pediatr Blood Cancer.* 2007.<sup>9</sup>

## CURRENT TREATMENT OPTIONS

The treatment for HLH has evolved over the years. According to the revised HLH 2004 guidelines<sup>7</sup>, treatment for HLH has a two-pronged approach, a short term strategy to control the hyperinflammatory state and a long term strategy aimed at curative approach by allogeneic hematopoietic stem cell transplantation (HSCT).

- Initial therapy (weeks 1–8)
  - Etoposide
  - Cyclosporine A
  - Dexamethasone
  - Gastroprotecting agents like ranitidine or pantaprazole
- Supportive therapy
  - Prophylactic cotrimoxazole
  - Oral antifungal
  - Intravenous immunoglobulins
  - Antivirals if ongoing infections
  - Broad spectrum antibiotics till culture reports are available
  - H2 receptor antagonists
- Continuation therapy: Patients without a family history of HLH and without genetic evidence of the disease are recommended to start continuation therapy if the disease is active after the initial therapy. Increasing disease activity may make it necessary to intensify the treatment in some children. It is from week 9 onwards till HSCT.
- Reactivation: If the patient develops a reactivation, intensification of therapy is recommended. Intrathecal therapy is recommended in cases of CNS-reactivation. Supportive antimicrobial, antiviral and antifungal therapy should be considered. HSCT should be considered in this group.
- Salvage therapy: In advanced disease:
  - Removal of cytokines via plasmapheresis
  - Recombinant human thrombopoietin

- Monoclonal antibodies such as alemtuzumab, infliximab, and daclizumab
- Etanercept, a TNF inhibitor
- HSCT: The only curative treatment available to date is HSCT.

## EFFICACY and SAFETY

<b>Trial</b>	NCT03312751, NI-0501-09; children up to 18 years; emapalumab as monotherapy in addition to current standard of care; phase III
<b>Sponsor</b>	NovImmune SA
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry <sup>5</sup>
<b>Location</b>	Not listed
<b>Design</b>	Open label, single group assignment
<b>Participants</b>	n= 34 (planned); aged up to 18 years; primary haemophagocytic lymphohistiocytosis with active disease; treatment naïve patients or patients having already received HLH conventional therapy, but having failed or unable to tolerate current standard of care
<b>Schedule</b>	Emapalumab will be administered by intravenous infusion, once every 3 days for the first 2 weeks, then twice weekly.
<b>Follow-up</b>	Active treatment for 8 weeks, follow-up up to 18 months
<b>Primary Outcomes</b>	Overall Response at Week 8 or End of Treatment (if earlier) [ Time Frame: Up to Week 8 ]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>● Overall Survival [Time Frame: Up to 18 months]</li> <li>● Number of patients proceeding to HSCT [Time Frame: Up to 18 months]</li> <li>● Change in PedsQL Score [Time Frame: Up to 18 months]</li> <li>● Incidence, severity, causality and outcomes of AEs (serious and non-serious) [Time Frame: Up to 18 months]</li> <li>● Immunogenicity [Time Frame: Up to 18 months]</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Primary completion date reported as June 2019

<b>Trial</b>	NCT01818492, NI-0501-04; children, emapalumab as monotherapy in addition to current standard of care (a glucocorticosteroid); phase II/III
<b>Sponsor</b>	NovImmune SA
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry <sup>16</sup>
<b>Location</b>	EU (incl UK) and the US
<b>Design</b>	Open label, single group assignment
<b>Participants</b>	n= 32 (planned); aged up to 18 years; primary haemophagocytic lymphohistiocytosis, Patient (if ≥ 18 years old)

<b>Schedule</b>	Emapalumab will be administered by intravenous infusion, twice weekly.
<b>Follow-up</b>	Active treatment for 12 weeks
<b>Primary Outcomes</b>	Overall response rate [Time Frame: end of treatment]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>• Time to response [Time Frame: any time during the study]</li> <li>• Durability of response [Time Frame: any time during the study]</li> <li>• Survival [Time Frame: end of the study and beyond]</li> <li>• Glucocorticoid tapering [Time Frame: any time during the study]</li> <li>• Safety and tolerability of NI-0501 in haemophagocytic lymphohistiocytosis [Time Frame: up to end of the study]</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Primary completion date reported as Dec 2017

## ESTIMATED COST and IMPACT

### COST

The cost of emapalumab is not yet known.

### IMPACT – SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
  Reduced symptoms or disability
- Other: *specify, e.g. improved quality of life for carers, improved patient convenience, wider societal benefits (e.g. earlier return to normal activities, including employment) etc.*
 No impact identified

#### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services
  Decreased use of existing services
- Re-organisation of existing services
  Need for new services
- Other
  None identified

#### IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs                       Reduced drug treatment costs
- Other increase in costs                                       Other reduction in costs
- Other: *uncertain unit cost compared to existing treatments*                       None identified

## OTHER ISSUES

- Clinical uncertainty or other research question identified                       None identified

## REFERENCES

- <sup>1</sup> Kaplon H and Reichert JM. Antibodies to watch in 2018. *mAbs*. 2018; 0(0), 1-21. Available from: <http://www.tandfonline.com/doi/pdf/10.1080/19420862.2018.1415671?needAccess=true> [Accessed on 5 February 2018]
- <sup>2</sup> Novimmune. *Emapalumab*: NI-0501. Available from: <https://www.novimmune.com/en/pipeline/emapalumab-ni-0501.html> [Accessed on 5 February 2018]
- <sup>3</sup> Schram AM and Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood*; 2015. 125(19):2908-2914. Available from: <http://www.bloodjournal.org/content/125/19/2908.long?sso-checked=true> [Accessed on 5 February 2018]
- <sup>4</sup> Global Data. *Emapalumab*. Available from: <https://pharma.globaldata.com/> [Accessed on 5 February 2018, log in required]
- <sup>5</sup> ClinicalTrials.gov. *Study to Assess the Efficacy and Safety of Emapalumab in Primary Haemophagocytic Lymphohistiocytosis*. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT03312751> [Accessed on 5 February 2018]
- <sup>6</sup> Jordan M, Locatelli F, Allen C, De Benedetti F, Grom AA et al. A Novel Targeted Approach to the Treatment of Hemophagocytic Lymphohistiocytosis (HLH) with an Anti-Interferon Gamma (IFN $\gamma$ ) Monoclonal Antibody (mAb), NI-0501: First Results from a Pilot Phase 2 Study in Children with Primary HLH. *Blood*. 2015; 126(23):LBA-3. Available from: <http://www.bloodjournal.org/content/126/23/LBA-3?sso-checked=true> [Accessed on 23 February 2018]
- <sup>7</sup> Ramachandran S, Zaidi F, Aggarwal A and Gera R. Recent advances in diagnostic and therapeutic guidelines for primary and secondary hemophagocytic lymphohistiocytosis. *Blood Cells Mol Dis*. 2017;64: 53-57. Available from: <https://www.sciencedirect.com/science/article/pii/S1079979616301887> [Accessed on 5 February 2018]
- <sup>8</sup> Hayden A, Park S, Giustini D, Lee AYY and Chen LYC. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review. *Blood Reviews*. 2016; 30(6):411-420. Available from: <https://www.sciencedirect.com/science/article/pii/S0268960X16300194> [Accessed on 5 February 2018]
- <sup>9</sup> Henter J, Horne A, Arico M, Egeler M, Filipovich AH et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*. 2007 Feb;48(2):124-131. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/pbc.21039/epdf> [Accessed on 5 February 2018]
- <sup>10</sup> Rosado FGN and Kim AS. Hemophagocytic Lymphohistiocytosis: An Update on Diagnosis and Pathogenesis. *Am J Clin Pathol*. 2015; 139(6):713-727. Available from: <https://academic.oup.com/ajcp/article/139/6/713/1765956> [Accessed on 5 February 2018]
- <sup>11</sup> Histiouk. *What is Haemophagocytic Lymphohistiocytosis (HLH)?* Available from: <http://www.histiouk.org/haemophagocytic-lymphohistiocytosis-hlh-in-children/> [Accessed on 5 February 2018]

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- <sup>12</sup> Gholam C, Grigoriadou S, Gilmour KC and Gaspar HB. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. *Clin Exp Immunol*. 2011 Mar; 163(3): 271–283. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3048610/> [Accessed on 5 February 2018]
- <sup>13</sup> Henter J, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002 100(7); 2397-2373. Available from: <http://www.bloodjournal.org/content/bloodjournal/100/7/2367.full.pdf?sso-checked=true> [Accessed 19 February 2018]
- <sup>14</sup> Henter J, Horne A, Arico M, Egeler RM, Filipovich AH et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*. 2006. Available from: <http://www.blf.net/onko/page4/page29/page30/files/HLH-2004%20PBC.pdf> [Accessed 19 February 2018]
- <sup>15</sup> Office for National Statistics. *Hospital Episode Statistics. Primary diagnosis: 34 character 2016-17*. Available from: <https://www.ons.gov.uk/> [Accessed on 5 February 2018]
- <sup>16</sup> ClinicalTrials.gov. *A Study to Investigate the Safety and Efficacy of an Anti-IFN $\gamma$  mAb in Children Affected by Primary Haemophagocytic Lymphohistiocytosis*. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT01818492> [Accessed on 5 February 2018]