NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MAY 2021

LAM-561 in addition to radiation therapy and temozolomide for glioblastoma –adjuvant

NIHRIO ID	29360	**NICE ID**	10607
Developer/Company	Laminar Pharma	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase II/III clinical trials

SUMMARY

LAM-561 in addition to radiation therapy and temozolomide is in development as a treatment option for newly diagnosed glioblastoma patients. Glioblastoma is a fast-growing brain tumour that develops from glial cells in the brain, is an aggressive brain cancer that typically results in death within months following diagnosis if not treated. Brain cancers are the ninth most common cancers in the UK; gliomas, of which glioblastoma is a type of, contribute to about one third of brain tumours. Current therapies remain palliative and include surgery to remove as much of the tumour as possible, followed by chemotherapy and/or radiation therapy. Glioblastoma represents a highly unmet medical need due to its dismal prognosis, meaningful disability and lack of new agents.

LAM-561 is in development as a new oral treatment for newly diagnosed glioblastoma. It mimics the structure of oleic acid, a fatty acid, and can cross the blood brain barrier to influence the environment within brain cells; importantly, LAM-561 does not affect healthy cells and only targets tumour cells. If licensed, LAM-561 would provide an additional treatment options for patients diagnosed with glioblastoma.

PROPOSED INDICATION

Treatment of adult patients with new diagnosed, isocitrate dehydrogenase isozyme 1 (IDH1) wildtype glioblastoma.[1]

TECHNOLOGY

DESCRIPTION

LAM-561(2-hydroxyoleic acid; 2-OHOA) is a synthetic derivative of oleic acid which can be taken orally and is able to reach cells in the brain by crossing the blood brain barrier. Inside the cell, LAM-561 is an activator of sphingomyelin synthase 1 (SMS1), a key enzyme that regulates phospholipid concentrations, particularly sphingolipids (SM) and phosphatidylethanolamine (PE), at the plasma membrane. The high proliferation rate of gliomas and other cancer cells is a key event in their tumorigenic transformation. SMS activation by LAM-561 restores the SM and PE levels in cancer cell membranes to those found in normal cells. By contrast, 2OHOA does not alter the lipid profile of normal cells, in which the relatively high levels of SM, the product of SMS, and the low levels of PE, the substrate of SMS, maintain SMS activity unaltered. Thus, 2OHOA shows lack of toxicity at therapeutic doses in vitro, in vivo and in humans (phase I/IIA trial), only acting in tumour cells. LAM-561 alters the composition of the plasma membrane in cancer cells, reducing the activity of membrane-associated signalling proteins that are known to promote tumour growth.[2,3]

LAM-561 is currently in development for the treatment of glioblastoma. In a phase II/III trial (NCT04250922), LAM-561 is administered orally, daily, from day one of week three to the end of the phase, in combination with temozolomide administered orally at 75mg/m2 for a maximum of 49 days and focal radiotherapy five days per week over six weeks (and for no more than seven weeks). The start of the first cycle during the maintenance phase is scheduled ~28 days (and never more than 42 days) after the last day of chemoradiation. During the maintenance phase, participants receive oral temozolomide-200 mg/m2 once daily on days 1-5 of each 28- day cycle for 6 cycles and LAM-561. Patients will continue to receive LAM-561 after cycle six of the monotherapy phase until end of study. Adjuvant treatment will be discontinued upon determination of tumour progression, unacceptable toxicity or refusal to continue study treatment.[1]

INNOVATION AND/OR ADVANTAGES

Membrane lipid composition and organisation is known to be significantly altered in cancer cells and it has been observed that these changes increase recruitment to the cell membrane of proliferation signalling proteins, such as K-Ras. Aberrant activity of Ras-associated proliferative signalling pathways is found in at least one third of all human cancers. LAM-561 induces translocation of K-Ras from its active domain in the plasma membrane, inactivating key Ras-dependent proliferation pathways (like Ras/MAPK, Pi3K/AKT/mTOR or PKC/Cyclin CDK). This causes endoplasmic reticulum stress, cell cycle arrest and eventually selective death of cancer cells in approximately 50% of the human cancer cell lines studied, and a similar proportion of patients treated with LAM-561.[2,4]

In phase I trials, LAM-561 as a monotherapy was found to have a good safety profile as well as promising clinical activity.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

LAM-561 does not currently have Marketing Authorisation in the EU/UK.

Temozolomide is currently indicated for the treatment of: [6]

- Adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as a monotherapy treatment
- Children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy

LAM-561 was awarded EMA Orphan Drug Designation for the treatment of glioma in 2011.[7]

LAM-561 is currently in clinical development in phase I/II trials for paediatric glioblastoma and advanced solid tumours.[8]

PATIENT GROUP

DISEASE BACKGROUND

Gliomas are brain tumours that start in glial cells. These are the supporting cells of the brain and the spinal cord. There are different types of gliomas. The most common type is called astrocytoma. Astrocytomas develop from a type of glial cells called astrocytes. Astrocytes are star shaped cells. They support the nerve cells (neurones) in the brain. Astrocytomas can be low grade (slow growing) or high grade (fast growing). There are 4 main types:[9]

Low grade

- pilocytic astrocytoma (grade 1)
- diffuse astrocytoma (grade 2)

High grade

- anaplastic astrocytoma (grade 3)
- glioblastoma (grade 4)

Around 80% of astrocytomas diagnosed yearly are grade 4 glioblastoma.

Symptoms of gliomas depends on the size, location and degree of infiltration of the tumour. They include headache, nausea, vomiting, seizures, visual disturbance, speech and language problems, and changes in cognitive and/or functional ability.[10]

Risk factors associated with brain tumours are age, overweight/obesity, medical radiation and a family history of tumours.[11] Three percent of brain and other central nervous system (CNS) tumours are preventable.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Brain tumours are relatively rare. In the UK in 2017, the proportion of brain tumours in relation to all new cancer cases was of 3%.[13] The age-standardised incidence rate in England is 18.7 per 100,000.[14] Brain, other CNS and intracranial tumours incidence is related to age, with the highest incidence rates being in older people. In the UK in 2015-2017, on average each year almost a quarter of new cases (23%) were in people aged 75 and over. In contrast to most cancer types, brain, other CNS and intracranial tumours also occur relatively frequently at younger ages. Age-specific incidence rates remain relatively stable from infancy to around age 25-29, before increasing steadily. The highest rates are in the 85 to 89 age group for females and the 80 to 84 age group for males.[15]

In England in 2017 there were a total of 4,568 registrations of newly diagnosed brain cancer, other central nervous system and intracranial tumours (ICD-10 code C71).[16] Around 33% of

all brain tumours are classified as gliomas.[17] Applying this number, around 1,507 cases of brain cancer were gliomas.

In the UK between 2016-2018, there were a total of 5,380 deaths attributed to brain tumours.[18] The age-standardised mortality rate in England is 8.7 per 100,000.[19] Latest published survival statistics (2018, patients diagnosed in 2013-2017) report a 1-year survival rate of 39.9% and 5-year survival rate of 12.2% (age-standardised).[20]

In England in 2019-2020, there were 16,971 hospital admissions with a primary diagnosis of neoplasm of brain (ICD-10 code C71) resulting in 92,805 bed days and 22,498 finished consultant episodes.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the UK, treatment of glioblastoma usually consists of surgical resection if possible, which may achieve either complete or partial resection of the tumour, although complete resection is rare. After surgery, radiotherapy with or without chemotherapy is used. If the size or position of the tumour means surgery is not possible without damaging surrounding tissue, radiotherapy and/or chemotherapy is offered.[22]

CURRENT TREATMENT OPTIONS

In England, NICE recommends temozolomide as an option for treating newly diagnosed glioblastoma in people with a World Health Organisation (WHO) performance status of 0 or 1 (where 0 refers to persons able to carry out all normal activity without restriction and 1 or a person restricted in strenuous activity but ambulatory and able to carry out light work). It also recommends carmustine implants for newly diagnosed high-grade glioma, but only for people in whom 90% or more of the tumour has been resected.[23]

PLACE OF TECHNOLOGY

If licensed, LAM-561 in combination with radiation therapy and temozolomide, will offer a novel treatment option for patients with newly diagnosed, IDH1 wildtype glioblastoma.

CLINICAL TRIAL INFORMATION

Trial	**CLINGLIO;** NCT04250922**;** A Randomized, Double-blind, Placebo-controlled Adjuvant Trial in Newly Diagnosed Primary Glioblastoma Subjects to Assess the Efficacy and Safety of 2-hydroxyoleic Acid (2-OHOA) in Combination With Radiotherapy and Temozolomide Standard of Care Treatment **Phase II/III** -active, not recruiting **Location(s):** EU (incl. UK) and Israel **Primary completion date:** April 2022
Trial design	Randomized, double-blinded, placebo controlled, parallel assignment
Population	Estimated N = 180; 18-75 years old; subjects with newly histologically confirmed intracranial malignant glioma that is

	IDH1 wildtype and who are scheduled to receive chemo-radiotherapy with temozolomide
Intervention(s)	• 2-OHOA – orally • Temozolomide – orally – 75mg/m^2 during chemotherapy phase, 150-200mg/m^2 during maintenance phase • Radiation Therapy - one treatment given daily 5 days per week over approximately 6 weeks
Comparator(s)	Matched placebo plus standard of care therapy
Outcome(s)	• To evaluate the efficacy of 2-OHOA in combination with the standard of care treatment of radiotherapy and temozolomide as assessed by progression free survival (PFS) using the Response Assessment in Neuro-Oncology (RANO) criteria • To evaluate the efficacy of 2-OHOA in combination with the standard of care treatment of radiotherapy and temozolomide, as assessed by overall survival See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of LAM-561 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (TA121). June 2007.
- NICE guideline. Brain tumours (primary) and brain metastases in adults (NG99). July 2018
- NICE interventional procedure guidance. Photodynamic therapy for brain tumours (IPG290). March 2009.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Brain/Central nervous system (Adult). B13/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Association of Neuro-Oncology (EANO). EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. December 2020.[24]

- Medical Oncology Spanish Society (SEOM). SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017). October 2017.[25]
- ESMO. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2014.[26]
- NICE pathway. Brain cancer: glioma. 2007.[27]

ADDITIONAL INFORMATION

Laminar Pharma did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 ClinicalTrials.gov. *2-OHOA With RT and TMZ for Adults With Glioblastoma (CLINGLIO). Trial ID: NCT04250922*. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04250922 [Accessed 13 April 2021].

2 Laminar Pharma. *LAM-561 in cancer*. Available from: https://laminarpharma.com/products_/#LP561A1 [Accessed 13 April 2021].

3 CLINGLIO. *PROJECT*. Available from: https://clinglio.eu/project.php [Accessed 13 April 2021].

4 Fernández-García P, Rosselló CA, Rodríguez-Lorca R, Beteta-Göbel R, Fernández-Díaz J, Lladó V, et al. The Opposing Contribution of SMS1 and SMS2 to Glioma Progression and Their Value in the Therapeutic Response to 2OHOA. *Cancers*. 2019;11(1). Available from: https://doi.org/10.3390/cancers11010088.

5 Laminar Pharma. *Final results of the MIN-001-1203 study with 2OHOA in oncology presented at ASCO 2017 annual meeting in Chicago*. Available from: https://laminarpharma.com/final-results-of-the-min-001-1203/ [Accessed 13 April 2021].

6 Electronic Medicines Compendium (eMC). *Temodal Capsules*. Available from: https://www.medicines.org.uk/emc/product/1463/smpc [Accessed 13 April 2021].

7 European Medicines Agency (EMA). *Public summary of opinion on orphan designation*. 2011. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/03/11/916-public-summary-opinion-orphan-designation-2-hydroxyoleic-acid-treatment-glioma_en.pdf [Accessed 13 April 2021].

8 ClinicalTrials.gov. *4 Studies found for: 2-OHOA | Phase 1, 2*. Available from: https://clinicaltrials.gov/ct2/results?term=2-OHOA&age_v=&gndr=&type=&rslt=&phase=0&phase=1&Search=Apply [Accessed 13 April 2021].

9 Cancer Research UK. *Astrocytoma and glioblastoma (GBM)*. Available from: https://www.cancerresearchuk.org/about-cancer/brain-tumours/types/astrocytoma-glioblastoma-multiforme [Accessed 13 April 2021].

10 Cancer Research UK. *Symptoms*. Available from: https://www.cancerresearchuk.org/about-cancer/brain-tumours/symptoms [Accessed 13 April 2021].

11 Cancer Research UK. *Risks and causes of brain tumours*. Available from: https://www.cancerresearchuk.org/about-cancer/brain-tumours/risks-causes [Accessed 13 April 2021].

12 Cancer Research UK. *Brain, other CNS and intracranial tumours risk factors*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-

type/brain-other-cns-and-intracranial-tumours/risk-factors#heading-Three [Accessed 13 April 2021].
13 Cancer Research UK. *Brain, other CNS and intracranial tumours incidence statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/incidence [Accessed 13 April 2021].
14 Cancer Research UK. *Brain, other CNS and intracranial tumours incidence by sex and UK country.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/incidence#collapseZero [Accessed 13 April 2021].
15 Cancer Research UK. *Brain, other CNS and intracranial tumours incidence by age.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/incidence#heading-One [Accessed 13 April 2021].
16 Office for National Statistics (ONS). *Cancer Registration Statistics, England, 2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Downloaded 10 August 2020].
17 John Hopkins Medicine. *Gliomas.* Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/gliomas#:~:text=Glioma%20is%20a%20common%20type,astrocytes%2C%20oligodendrocytes%20and%20ependymal%20cells. [Accessed 13 April 2021].
18 Cancer Research UK. Brain, other CNS and intracranial tumours statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours [Accessed 13 April 2021].
19 Cancer Research UK. *Brain, other CNS and intracranial tumours mortality by sex and UK country.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/mortality#collapseZero [Accessed 13 April 2021].
20 Office for National Statistics (ONS). *Cancer Survival in England - adults diagnosed: 2013 - 2017 (followed up in 2018)*. Available from: https://www.ons.gov.uk/file?uri=%2fpeoplepopulationandcommunity%2fhealthandsocialcare%2fconditionsanddiseases%2fdatasets%2fcancersurvivalratescancersurvivalinenglandadultsdiagnosed%2f20132017/adultcancersurvivaltables.xlsx [Downloaded 10 August 2020].
21 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20
22 National Institute for Health and Care Excellence. *Health Technology Appraisal: Depatuxizuman mafodotin for treating recurrent EGFR-amplified glioblastoma.* Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10242 [Accessed 13 April 2021].
23 National Institute for Health and Care Excellence. *Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.* Available from: https://www.nice.org.uk/guidance/ta121/chapter/1-Guidance [Accessed 13 April 2021].
24 Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nature Reviews Clinical Oncology*. 2021 2021/03/01;18(3):170-86. Available from: https://doi.org/10.1038/s41571-020-00447-z.
25 Martínez-Garcia M, Álvarez-Linera J, Carrato C, Ley L, Luque R, Maldonado X, et al. SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017). *Clinical and Translational Oncology*. 2018 2018/01/01;20(1):22-8. Available from: https://doi.org/10.1007/s12094-017-1763-6.
26 Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up &#x2020. *Annals of Oncology*. 2014;25:iii93-iii101. Available from: https://doi.org/10.1093/annonc/mdu050.
27 National Institute for Health and Care Excellence. *Brain cancer: glioma.* Available from: https://pathways.nice.org.uk/pathways/brain-tumours-and-metastases#path=view%3A/pathways/brain-tumours-and-metastases/brain-cancer-glioma.xml&content=view-index [Accessed 13 April 2021].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.