



## Committee for Orphan Medicinal Products

### Public summary of positive opinion for orphan designation of

### HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor for the treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients

On 21 June 2004, orphan designation (EU/3/04/202) was granted by the European Commission to CellCure ApS (currently CellCure A/S), Denmark, for HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor for the treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients.

#### **What is MART-1 positive malignant melanoma in HLA-A2 positive patients?**

Malignant melanoma is a cancer of the pigmented melanocytes, cells mostly found in the skin (e.g. in moles), but also present in many other organs, e.g. the eye and mucous membranes. Melanoma usually occurs in adults and adolescents. MART-1 (Melanoma Antigen Recognized by T cells) is a protein expressed on the surface of normal melanocytes and is almost always present in melanoma cells.

MART-1 can be recognised by cells responsible for the immune response like T-cells.

HLA stands for human leukocyte antigen and cell surface receptors that are recognised by cells of the immune system. Recognition of HLA by the immune system gives the cell its identity as a member of the organism. On the contrary, any cell with an HLA recognised as foreign would trigger an immune response against it. HLA-A2 is one of the different types of leukocyte antigens that have been described in humans.

Malignant melanoma is life threatening, in particular due to poor survival in advanced stages of the disease.

#### **What is the estimated number of patients affected by the condition?**

At the time of designation MART-1 positive malignant melanoma affected 3.6 in 10,000 people in the European Union (EU)\*. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP). This is below the threshold for orphan designation which is 5 in 10,000. This is equivalent to a total of around 139,000 people.

#### **What treatments are available?**

Surgery is the first treatment applied to melanoma. There are also pharmacologic treatments that have been authorised in the Community for the treatment of melanoma. The choice of treatment depends on the extent of the melanoma lesion. Treatments include several medicinal products aimed at killing cancer cells (vincristine, dacarbazine, carmustine) or at stimulating an immune reaction against them (interferon-alpha). HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor might be of potential significant benefit for the treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients. This medicinal product could represent an additional treatment for use in combination with other treatments, and eventually improve the long-term outcome of the patients. The

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\*Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 385,000,000 (Eurostat 2002) and may differ from the true number of patients affected by the condition.

assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

### **How is this medicine expected to work?**

This medicinal product is essentially a group of specialised cells of the immune system (body's defence mechanism against infection and disease) designed to bear on their surface the subtype A2 of the HLA-A and the receptor for the melanoma protein MART-1. On the cell surface, these cells also carry a molecule called CD8 which is involved in the activation of the immune system. This way, these cells are expected to attack only melanoma cells expressing MART-1 in HLA-A2 patients. After binding to MART-1, these immune cells are expected to destroy melanoma cells.

### **What is the stage of development of this medicine?**

The effects of HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in HLA-A2 positive patients with were ongoing.

HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor was not marketed anywhere worldwide for MART-1 positive malignant melanoma in HLA-A2 positive patients or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 14 May 2004 a positive opinion recommending the grant of the above-mentioned designation.

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Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the Community) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

### **For more information:**

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**Translations of the active ingredient and indication in all EU languages  
and Norwegian and Icelandic**

<b>Language</b>	<b>Active Ingredient</b>	<b>Indication</b>
English	HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor	Treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients
Czech	HLA-A2 CD8 T lymfocyty exprimující Mart-1 T-buněčný receptor	Léčba MART-1 pozitivního maligního melanomu u HLA-A2 pozitivních pacientů
Danish	HLA-A2 restriktiv CD8 T-celle line koding for MART-1 receptor	Behandling af MART-1 positive malignt melanom hos HLA-A2 positive patienter
Dutch	HLA-A2 positieve CD8 T-cel lijn met uitdrukking van MART-1 T-cel receptor	Behandeling van MART-1 positief melanoom in HLA-A2 positieve patiënten
Estonian	HLA-A2 alatüübiga CD8 T-rakud, mis omavad Mart-1 T-rakkude retseptorite ekspressiooni	Halvaloomulise MART-1 positiivse melanoomi ravi HLA-A2 positiivsetel patsientidel
Finnish	HLA-A2 rajoittuva CD8 T-solulinjaa ilmaiseva MART-1 reseptori	MART-1 positiivisen pahanlaatuisen melanooman hoitoon HLA-A2 positiivisilla potilailla
French	Lignée de cellules lymphocytaires T CD8 HLA-A2 positive exprimant le récepteur à l'antigène MART-1 des cellules malignes lymphocytaires T	Traitement du mélanome exprimant MART-1 chez des malades porteurs de l'antigène HLA-A2
German	HLA-A2 positive, MART-1 kodierende CD8 T-Zelllinie, ,	Zur Behandlung des MART-1 positiven malignen Melanoms bei HLA-A2 positiven Patienten
Greek	Τ-κυτταρική σειρά περιορισμένη σε HLA-A2 η οποία κωδικοποιεί τον υποδοχέα Mart-1	Θεραπεία του θετικού σε Mart-1 κακοήθους μελανώματος σε HLA-A2 θετικούς ασθενείς
Hungarian	MART-1 sejtekre specifikus HLA-A2 restriktívot mutató CD8 T -sejtvonal	MART- 1 pozitív -malignus melanoma kezelése HLA-A2 pozitív betegek esetében
Latvian	HLA-A2 ierobežota CD8 T šūnu līnija ar specifiskumu pret Mart-1 T šūnu receptoru	MART-1 pozitīvas ļaundabīgas melanomas ārstēšana HLA-A2 pozitīviem pacientiem
Lithuanian	Su ŽLA-A2 susijusi CD8 T-ląstelių linijos ekspresija MART-1 T-ląstelių receptoriui	Pacientų, turinčių ŽLA-A2, piktybinės MART – 1 teigiamos melanomos gydymas
Maltese	HLA-A2 restricted CD8 T-cell line expressing MART-1 T-cell receptor	Treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients
Polish	Ograniczone HLA-A2 komórki T linii CD8 z ekspresją MART-1 receptorów T-komórkowych	Leczenie czerniaka złośliwego z dodatnim MART-1 u pacjentów z dodatnim HLA A2
Portuguese	Células T CD8 HLA-A2	Tratamento do melanoma maligno positivo ao

	positivas que expressam o receptor de células T para MART-1	MART-1 em doentes HLA-A2 positivos
Slovak	HLA-A2 CD8 T lymfocyty exprimujúce Mart-1 T-bunkový	Liečba MART-1 pozitívneho malígneho melanómu u HLA- A2 pozitívnych pacientov
Slovenian	HLA-A2 citotoksična T-celična veriga s specifičnim receptorjem za MART-1	Zdravljenje MART-1 pozitivnega malignega melanoma pri HLA-A2 pozitivnih bolnikih
Spanish	Células T CD8 con restricción HLA-A2 que expresan el receptor de células T para MART-1	Tratamiento del melanoma maligno positivo para MART-1 en pacientes HLA-A2 positivos
Swedish	HLA-A2 restriktiv CD8 T-cellslinje kodande för MART-1 T-cellsreceptorn.	Behandling av MART-1 positivt malignt melanom hos HLA-A2 positiva patienter
Norwegian	HLA-A2 forlikelig cytotoksisk (CD8) T-cellelinje som uttrykker T-cellereseptor spesifikk for MART-1	Behandling av MART-1 positivt malignt melanom hos HLA-A2 positive pasienter
Icelandic	HLA-A2 frumudrepandi T-frumu lína (CD8) sem tjáir MART-1 T frumu viðtaka	Meðferð við MART- 1 jákvæðu sortukrabbameini hjá HLA-A2 jákvæðum sjúklingum