Improving patient access to gene and cell therapies for rare diseases in Europe

A review of the challenges and proposals for improving patient access to advanced therapeutic medicinal products in Sweden

V1

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Chaired by:

Secretariat support by:

Reader notes:

This document contains country-specific insights on challenges and potential solutions to patient access to advanced therapeutic medicinal products (ATMPs) for patients with rare diseases.

The purpose of the document is to provide a starting point for country-specific engagement and discussion within multi-stakeholder meetings.

The challenges and solutions were discussed and prioritised with members of the RARE IMPACT Working Group in meetings and WebEx's between September 2018 and September 2019. Country-specific challenges/solutions have drawn on global recommendations previously published by EUCOPE and ARM, both members of the Working Group.

The challenges and solutions contained within this document are those that have been proposed as priorities for discussion with local stakeholders by members of the Working Group – the report does not include all challenges identified during the secondary research or Working Group meetings.

Contents

Executive Summary

The RARE IMPACT initiative was launched at the European Conference on Rare Diseases and Orphan Products in 2018. It is a multi-stakeholder initiative working to improve patient access to gene and cell therapies (or advanced therapy medicinal products [ATMPs])[1]. This patient-focused initiative aims to both assess challenges and propose actionable solutions to concerns regarding patient access to these transformative rare disease treatments in Europe. Through engagement with health technology assessment (HTA) agencies, regulatory bodies, payers, patient groups, clinicians, manufacturers and other experts across Europe, RARE IMPACT partners have proposed ideas to provide better access to ATMPs in Europe.

Access to ATMPs in Sweden has been challenging to date. Agreement on Yescarta required a rebate to regional budget holders, Kymriah was not recommended for one of its two indications, while Luxturna and Alofisel are not recommended by the New Therapy (NT) Council based on the health economic assessment of the products. In order to secure sustainable access, challenges in the assessment process for ATMPs should be addressed as a priority.

Flexibility in the assessment process for ATMPs is needed without compromising the integrity and rigour of the current assessment process. As with other HTA/cost-effectiveness analysis (CEA) markets, the major challenge for ATMPs in Sweden is the quality of evidence, the ability to extrapolate from short-term, surrogate endpoints to outcomes, indirect comparison, and the cost of comparator treatments. The Tandvårds-läkemedelsverket (TLV) conducts value-based pricing assessments, which in theory could be helpful to potentially curative treatments for rare diseases. There is some flexibility in the TLV ICER threshold, which reflects the three principles of the assessment process; human value, needs & solidarity and cost-effectiveness. The willingness to pay can therefore differ on a case-by-case basis based on the first two principles, and higher ICER thresholds can be provided for treatments for rare diseases with high unmet need. Nonetheless, even with this additional flexibility, TLV's ICER thresholds are often insufficient for orphan medicines and such drugs have been rejected by the TLV in the past. After the Cerezyme & Vpriv assessments, the TLV concluded that under certain circumstances they can find it appropriate to allow the rarity of a disease to motivate a higher cost in comparison to the benefit the treatment gives. Taking other factors into account, the TLV concluded it might then be reasonable to accept a cost of up to SEK2M (€180,000) per QALY.

The assessment route is also evolving in Sweden. TLV does not always assess inpatient-only drugs; for these treatments, funding decisions may be taken by individual regions or on recommendation from the NT Council. To date, reimbursement decisions for ATMPs have been taken for individual regions by the NT Council. If an orphan product is not recommended by the NT council, the regions cannot subsequently fund it.

As funding decisions in Sweden can be influenced by medical need there may be a willingness to pay for treatments for conditions that are very rare and/or have severe unmet need. Budgets are held by regions and the high-cost ATMPs' patient populations could be unequally distributed across the country, representing a funding challenge for individual regions (particularly smaller ones). However, exemptions are made between regions whereby if some conditions are more prevalent in some areas, costs can be shared, and this could potentially be a model that could be applied for ATMPs for rare conditions in the future.

Tripartite negotiations are in some cases possible between the TLV, NT Council and manufacturers, which provides an opportunity for dialogue on more innovative contractual arrangements. In general, there has been little experience with outcomes-based contracting in Sweden nor with staggered payments. A new programme to manage the introduction of new therapies has been developed which

[1] Medicines for human use developed from genes, cells or tissues are classified as ATMPs by the European Medicines Agency (EMA)

will enhance monitoring of new medicines and collect data that can impact cost-effectiveness and possibly form part of outcomes-based contracting. Further, a recent government funded report reviewing the current financing, subsidy and pricing systems for pharmaceuticals has made recommendations for funding ATMPs. The report proposes a special state contribution to regions to support the use of certain new pharmaceutical areas, such as ATMPs. The government are currently reviewing stakeholder comments before any processes are put in place for this funding route.

When products are not funded nationally or in a home region in Sweden, patients have previously received access to treatment via cross-border initiatives (E112) and in other local regions. While positive for these patients, the sustainability of making products available on case-by-case basis is challenging. A national level initiative would facilitate patients' access to treatments in accredited centres in other regions, eliminate economic burden of unequally distributed patient populations across the country and remove potential disincentives of referrals outside of the region.

Accessibility may present greater difficulties, particularly in the northern parts of Sweden, as ensuring proximity to a treatment centre could be challenging, given the size of the country. The Swelife-ATMP initiative aims to strengthen Sweden's preparedness for ATMPs, which could be leveraged to provide a solution to cross-regional patient transfer when expertise is concentrated in few treatment centres.

An overview of challenges and proposals for improving patient access to ATMPs in Sweden

Domain (Impact)*	Challenge	Proposed solution	Feasibility**
Assessment 	**AS1.** The assessment process is not accommodating of the data that are generated in trials for ATMPs	**AS1a.** The TLV should assess applicability of current process to ensure flexibility for ATMP assessment	++
		AS1b. Proposals should be brought forward on integration of ATMP-specific methods into the assessment process	++
	AS2. Decisions on ATMP access are de-centralised to regions	**AS2.** A national-level assessment protocol for ATMPs that calls on the TLV, NT council and manufactures to participate in a tripartite assessment	++
Affordability 	**AF1.** Even with assessment at national level, budgets are held by regions	**AF1.** Encourage establishment of state contribution as recommended in a recent report on pharmaceutical financing	++
	AF2. There is limited experience with innovative payment options and the current structure is incentivising long-term treatments over cures	**AF2a.** Remove barriers to annuity payments and link with outcomes to better allow councils to address budget impact concerns	+
		AF2b. Leverage regional experience of managed entry agreements and the IHE recommendation for an outcomes-based approach	+++
Availability 	**AV1.** Cross-border and cross-regional treatments is a legal right, but in practise it might be a challenge in Sweden	**AV1.** Enable a national level initiative to facilitate access to accredited treatment centres	+
Accessibility 	**AC1.** Proximity to a treatment centre could present a geographic barrier	**AC1.** Harness willingness to invest in infrastructure and training to identify cross-county council solutions	+
	AC2. ATMPs may require novel surgical or non-surgical administration devices or protocols	**AC2.** Early communication with the TLV on likelihood of need for assessment of delivery process	+

Notes: *The working group assessment of the relative impact of the challenge of each domain on patient access is represented by Harvey balls from highest (represented by a full blue Harvey ball) to lowest (represented by an empty, white Harvey ball); **Feasibility: Working Group assessment of feasibility of solutions to be implemented. + low feasibility, ++ medium feasibility, +++ high feasibility

The collaboration

RARE IMPACT is a collaboration of three not-for-profit organisations, two trade associations and 18 manufacturers of ATMPs brought together by EURORDIS, a non-governmental patient-driven alliance of patient organisations. The overarching objective of the collaboration is to ensure European patients with rare diseases obtain quick access to gene and cell therapies and to create a sustainable model for manufacturers and payers to maintain patient access and innovation. To achieve this objective, the collaboration has established the following goals:

- Identify challenges that are preventing rare disease patients accessing ATMPs
- Propose actionable solutions to address these challenges
- Utilise these ideas within multi-stakeholder discussions within individual countries and in pan-regional forums

The approach

A framework for categorising barriers to patient access was developed and validated by the collaboration. The framework includes four categories, described in **Error! Reference source not found.** below.

Table 1. Framework applied to structuring identified challenges

Category	Description
Assessment (magnitude of benefit)	Challenges related to the assessment of the benefit of ATMPs within pricing and reimbursement processes. This includes topics such as evidence uncertainty, generating comparative data, use of surrogate endpoints and assessment pathways
Affordability (price, cost and funding	Challenges concerning the pricing, funding and affordability of ATMPs, including the application of innovative payment models
Availability (legally available)	Non-regulatory challenges to the product being available within countries, such as those related to cross-border healthcare and hospital exemptions
Accessibility (accessible by patients)	Administrative, service capacity and geographic challenges that delay or prevent patient access to ATMPs

Identification of challenges and proposals for improving patient access

Primary and secondary research was conducted to identify challenges to patient access to ATMPs and potential solutions. Secondary research was conducted to create a database of conceptual and country-specific challenges. This research included:

- Reviewing outputs from other initiatives (e.g., ARM's "Recommendations for Timely Access to ATMPs in Europe" and EUCOPE's "Gene & Cell Therapy – Pioneering Access for Ground-Breaking Treatments")
- Assessing pathways through which patients access ATMPs in the countries of interest
- Reviewing HTA and P&R decisions for existing ATMPs

Challenges and potential solutions were supplemented, assessed and prioritised through a review process including:

- Members of the Working Group (including EURORDIS, trade associations, affiliated NGOs and 18 member companies)
- Country-specific patient associations
- Country level decision makers, such as policymakers, HTA bodies and budget holders
- Experts and advisors, such as healthcare professionals, patient representatives, P&R system experts, ATMP technical experts, economists and academics

In Sweden, stakeholders engaged included representatives from the NT council and patient representatives.

Following stakeholder engagement, the challenges and solutions were refined and prioritised to reflect the perceived importance in improving patient access and feasibility of implementation. Therefore, the challenges in this report are not exhaustive of all identified through primary and secondary research but represent the most important issues as determined by stakeholders.

The outputs from this process have been summarised in this report as a basis for discussion within multi-stakeholder meetings in each country and at European level.

ASSESSMENT

Impact: 

Challenge		Proposed solution		Feasibility
AS1.	The assessment process is not accommodating of the data that are generated in trials for ATMPs	**AS1a.**	The TLV should assess applicability of current process to ensure flexibility for ATMP assessment	++
		AS1b.	Proposals should be brought forward on integration of ATMP-specific methods into the assessment process	++
AS2.	Decisions on ATMP access are de-centralised to regions	**AS2.**	A national-level assessment protocol for ATMPs that calls on the TLV, NT council and manufactures to participate in a tripartite assessment	++

The working group assessment of the **impact** of the challenge relate to all challenges in each domain. The working group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified assessment challenges

Challenge AS1.

The assessment process is not accommodating of the data that are generated in trials for ATMPs.

In Sweden, pricing and reimbursement decisions are determined by cost-effectiveness analysis. ATMPs for rare diseases face major challenges within this quantitative assessment process due to the nature of the interventions and the type of evidence available at the time of appraisal. Gathering evidence on the long-term benefit of ATMPs is difficult due to small sample sizes, data derived from single arm studies, surrogate endpoints and lack of natural history data on the disease course. The TLV does, however, account for orphan status in their cost-effectiveness approach. This is demonstrated in the cost-effectiveness threshold based on three principles; unmet need, severity of condition and limited budget impact due to small populations. Additionally, the HTA perspective regarding economic analysis takes a broader societal perspective.

A national working group called the ‘Regional cooperation of cancer centres’ (Regionala Cancercentrum i Samverkan) aims to support the NT council during their assessments as well as acting as the coordination group in the process of enabling CAR-Ts in Sweden. For Yescarta, any discussions regarding use of the therapy will occur at the national level within the national level working group, to help identify suitable patients and coordinate the follow-up and evaluation of the therapy.

Proposed solution AS1a.

The TLV should assess applicability of current process to ensure flexibility for ATMP assessment.

The TLV have noted that there may be a need for flexibility in their assessment approach to ensure access to innovative products, such as ATMPs. This was borne out with the assessment of Yescarta; flexibility was shown in their approach to cost-effectiveness modelling where there was acceptance of the connection of surrogate measures to expected clinically relevant outcomes and for an ITC with historical cohort controls. This shows a willingness to adapt current assessment procedures when assessing ATMPs. By reviewing their HTA process in the context of ATMPs, the TLV could identify aspects that fit current requirements and potential changes that need to be implemented to ensure consistency in the process. Additionally, this review would indicate if the current ICER threshold would be acceptable for

ATMPs. Considering that Sweden conducts cost-effectiveness analyses from a broader societal perspective and has principles based on equal human value, it is possible that the therapies could be recommended even if the ICER is higher than the usual threshold. Once identified, the TLV should publicise the process for the assessment of ATMPs to enhance clarity. However, accomplishing such a change might necessitate political steer.

Feasibility: ++
Stakeholders: TLV, trade association
Timeline: 6–12 months

Proposed solution AS1b.

Proposals should be brought forward on integration of ATMP-specific methods into the assessment process.

In order to facilitate reform in the assessment of ATMPs, the TLV, the NT council and manufactures need to communicate on key requirements for data gathering that could facilitate the assessment of ATMPs. Proposals that could be brought forward include:

1. The acceptance of surrogate endpoints.
2. Incorporating data generated following initial assessment. This would reduce uncertainty in the clinical effectiveness assessment of the product, with review taking place over an extended duration rather than at a single point in time.
3. Specific technical solutions for extrapolating short-term data to inform decisions on the potential long-term benefit.
4. Incorporation of data from indirect treatment comparisons.

Feasibility: ++
Stakeholders: TLV, NT Council, trade associations, individual companies
Timeline: Immediate–12 months

Challenge AS2.

Decisions on ATMP access are de-centralised to regions.

During horizon scanning, the regions and the NT Council decide which products that should be assessed on the national level in the joint process and which should be evaluated individually by each region. An NT Council recommendation means regional negotiation is not required. However, if a positive NT recommendation is not achieved, negotiations with individual regions are not allowed.

Proposed solution AS2.

A national-level assessment protocol for ATMPs that calls on the TLV, NT council and manufactures to participate in a tripartite assessment.

Provide a clear national-level assessment protocol for ATMPs that calls on the TLV, NT council and manufactures to participate in a national level tripartite assessment and negotiation process to ensure consistency in the assessment of ATMPs.

Feasibility: ++
Stakeholders: TLV, NT Council, individual companies
Timeline: Immediate

AFFORDABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AF1.	Even with assessment at national level, budgets are held by regions	**AF1.**	Encourage establishment of state contribution as recommended in a recent report on pharmaceutical financing	++
AF2.	There is limited experience with innovative payment options and the current structure is incentivising long-term treatments over cures	**AF2a.**	Remove barriers to annuity payments and link with outcomes to better allow councils to address budget impact concerns	+
		AF2b.	Leverage regional experience of managed entry agreements and the IHE recommendation for an outcomes-based approach	+++

The working group assessment of the **impact** of the challenge relate to all challenges in each domain. The working group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified affordability challenges

Challenge AF1.

Even with assessment at national level, budgets are held by regions.

Pharmaceutical budgets are held by regions and given the possibility that ATMP eligible patients might be unequally distributed between these, high-cost ATMPs could represent a funding challenge for individual regions (particularly in smaller regions). Exemptions have been made between regions to share the costs if some conditions are more prevalent in some areas, but it is uncertain if these exemptions could be a potential solution in the future.

Proposed solution AF1.

Encourage establishment of state contribution as recommended in a recent report on pharmaceutical financing.

Tripartite negotiations have afforded county councils a greater stake in the price setting of pharmaceuticals included in the managed introduction process, and their willingness-to-pay is better represented. With Yescarta, the contract includes a “pay back after use” agreement which gives the county councils a confidential net price. While a positive step, this does not address the funding of ATMPs.

A recent government funded report reviewing the current financing, subsidy and pricing systems for pharmaceuticals has made recommendations for funding ATMPs. The report proposes a special state contribution to regions to support the use of certain new pharmaceutical areas, such as ATMPs. The motive for this is to create equal conditions across the country. Regarding the pricing of orphan medicinal products, the report considers that an increased willingness to pay may be needed in exceptional cases, but that it is important to continue to consider cost-effectiveness. Encouraging the establishment of this state contribution will remove the budget burden from individual regions, even though this is likely to be a time-consuming solution (as historically, state contributions have only been received as exemptions). The government are currently processing the report by reviewing external stakeholder comments and discussing it with the other departments. It was stated by the department of health that they are conducting the process thoughtfully, as these will be the first changes made since 1998.

Feasibility: ++
Stakeholders: TLV, NT Council
Timeline: Immediate – 6 months

Challenge AF2.

There is limited experience with innovative payment options and the current structure is incentivising long-term treatments over cures.

The current reimbursement structure incentivises long-term treatments over one-off treatment options. The national health care system in Sweden has legal restrictions for payments of consumables beyond three years and the system is not used to annuity payment. Thus, with current financing models there is a risk that the initial cost and the budget barrier will impact patient access. Similarly, there has been little experience with outcomes-based contracting. To date, the most common agreements are straight discounts due to a lack of experience with national registries and their administrative demands for outcomes-based agreements.

Proposed solution AF2a.

Remove barriers to annuity payments and link with outcomes to better allow councils to address budget impact concerns.

Removing the previously stated barriers to annuity payments could address this challenge. Instalments paid over a pre-agreed time period or linked to outcomes may be more manageable for the payer, enabling therapies to be paid for over time. In addition, payment via an annuity scheme would better reflect patient health gains whilst reducing uncertainty in data available at launch. Treated patients should be registered in local quality registries with regular follow-up appointments, and the data reported to the European Society for Blood and Marrow Transplantation (EBMT) patient records.

Feasibility: +
Stakeholders: TLV, Ministry of Health, specialist treatment centres
Timeline: Immediate

Proposed solution AF2b.

Leverage regional experience of managed entry agreements and the IHE recommendation for an outcomes-based approach.

Research conducted by ARM demonstrate that regions are showing a willingness to adapt reimbursement models for ATMPs. Currently for Yescarta, there is a “pay back after use” contract that gives the regions a confidential net price. Risk sharing agreements have been implemented in Sweden, but not specifically for orphan drugs. In order to pay for the ATMP treatments, the Institute of Health and Medical Economics (IHE) suggests a completely new model with payment based on a valuation of the medical outcomes. This new model would likely take time to implement, even if national funding is connected to it. However, leveraging county council experience of managed entry agreements combined with the IHE recommendation for an outcomes-based approach could provide a sustainable solution.

Feasibility: +++
Stakeholders: TLV, county councils
Timeline: 6–12 months

AVAILABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AV1.	Cross-border and cross-regional treatments is a legal right, but in practise it might be challenge in Sweden	**AV1**.	Enable a national level initiative to facilitate the patient's legal rights and enable access to the accredited treatment centres	+

The working group assessment of the **impact and importance** of the challenge relate to all challenges in each domain. The working group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working Group identified availability challenges

Challenge AV1.

Cross-border and cross-regional treatments is a legal right, but in practise it might be challenge in Sweden.

Patients from Sweden have previously received treatment in other countries via cross-border initiatives (E112) or in other regions in Sweden. Cross-border health care would therefore not be considered a novel option in Sweden. For example, in July 2019, it was announced that the Stockholm region would offer primary breast cancer radiation to other regions in Sweden and in Finland. This was done to ensure that the treatment is administered within the needed time frame of the disease, with the decision made due to early identification of resource shortages elsewhere. However, this is not perceived as common practise, as it could result in additional administrative hurdles and hospitals are not reimbursed for treatments conducted outside of the patient's own region, which could disincentivise the practise of these kinds of referrals.

Solution AV1.

Enable a national level initiative to facilitate the patient's legal rights and enable access to the accredited treatment centres.

To remove the potential hurdles identified, reimbursement for treatment should be moved from the regions to the national level. A national level initiative would accommodate patient access to ATMPs on multiple levels. Firstly, it would address the fact that only certain regions will have specialised and accredited centres where ATMPs can be administered (e.g., Karolinska University Hospital in Stockholm was the first hospital certified to treat patients with Kymriah in R/R post-ASCT B-ALL). Secondly, it would remove potential economic hurdles in the current systems that might disincentive referrals. Finally, it would also equalise the payment burden if the patient populations are unequally distributed across regions.

Feasibility: +
Stakeholders: TLV, county councils
Timeline: 6–12 months

ACCESSIBILITY

Impact: 

Challenge		Proposed solution		Feasibility
AC1.	Proximity to a treatment centre could present a geographic barrier	**AC1.**	Harness willingness to invest in infrastructure and training to identify cross-county council solutions	+
AC2.	ATMPs may require novel surgical or non-surgical administration devices or protocols	**AC2.**	Early communication with the TLV on likelihood of need for assessment of delivery process	+

The working group assessment of the **impact** of the challenge relate to all challenges in each domain. The working group assessment of **feasibility** relates to the individual or groups of proposed solutions.

Working group identified accessibility challenges

Challenge AC1.

Proximity to a treatment centre could present a geographic barrier.

Proximity to a specialist treatment centre may be a challenge in Sweden, particularly in the northern part of the country.

Proposed solution AC1.

Harness willingness to invest in infrastructure and training to identify cross-county council solutions.

Swedish stakeholders have highlighted a willingness to invest in infrastructure and training to ensure expertise is available “in-house” throughout the country. The Swelife-ATMP initiative aims to strengthen Sweden’s preparedness for ATMPs. The project aims to increase competence in ATMP delivery across Sweden, as this is acknowledged as a requirement for making Sweden attractive for ATMP delivery and development. While the primary focus is on education and preparedness, this initiative could potentially represent a route to identify cross-regional resources for ATMP delivery and to construct protocols for cross-regional patient transfer.

Feasibility: +
Stakeholders: County councils, specialist treatment centres
Timeline: 6–12 months

Challenge AC2.

ATMPs may require novel surgical or non-surgical administration devices or protocols.

ATMPs may require novel surgical or non-surgical administration devices or protocols, and these may in some cases require a separate HTA assessment before the medicinal product itself can be appraised. This could delay reimbursement negotiations and present additional complications.

Proposed solution AC2.

Early communication with the TLV on likelihood of need for assessment of delivery process.

Manufacturers are encouraged to engage with the regions' horizon scanning processes as soon as possible during the clinical development to inform them about any specific implications of the procedures or protocols that might be needed for a given ATMP. Horizon scanning interactions with regions occur once per year and cover approvals/launches with a 2-3-year scope. Subsequently, an early assessment report is developed that identifies the budget impact, required health care changes (in structures and processes) and competence needed. As not all regions will have treatment centres, national level preparations are required

Feasibility: ++
Stakeholders: Individual companies, county councils, TLV
Timeline: 6–12 months

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Appendix

Country profile:

Market type	Cost-effectiveness analysis
Position in launch sequence	Early

	Status	Note
Strimvelis	Not evaluated	
Holoclar	Not evaluated	
Zalmoxis	Not evaluated	
Glybera	Not evaluated	
Imlygic	Preliminary assessment[1]	
Provenge	Not evaluated	
MACI	Not evaluated	
ChondroCelect	Not evaluated	
Yescarta	Positive recommendation by NT council in DLBCL[2]	Recommended for patients with R/R DLBCL and PMBCL in 2L+ after the manufacturer agreed on returning some of the costs to the regions, making it cost-effective[2]
Kymriah	Positive recommendation by NT council in B-ALL[3] Negative recommendation by NT-council in DLBCL underway[4]	Recommended usage for patients up to 25 years of age with acute lymphocytic B-cell leukaemia (B-ALL) who are R/R after transplantation/at second or subsequent recurrence.[3] Not recommended for DLBCL due to uncertainty in the data.[4]
Luxturna	Negative recommendation[5]	The NT Council does not recommend Luxturna due to uncertainties in the health economic evaluation[5]
Alofisel	Negative recommendation[6]	The NT council does not recommend Alofisel based on the uncertainty of the long-term effect that impacts the health economic model, weighted with the overall assessment it is not recommended[5]
Zynteglo	Preliminary assessment[7]	
Zolgensma	Preliminary assessment[8]	

[1] NT Council. Imlygic. Available from: https://janusinfo.se/download/18.1dfa69ad1630328ad7c3908c/1535626617423/Talimogene-laherparepvec-vid-melanom-tidig-bedomnigsrapport-150511.pdf
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