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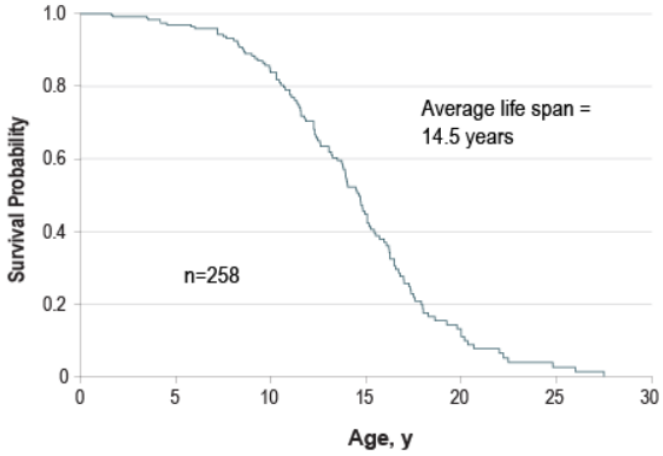
Formulation of Lonafarnib with cyclodextrins for better treatment of Hutchinson-Gilford progeria syndrome

Hutchinson-Gilford progeria

- Progeria is an extremely rare genetic disorder with symptoms resembling aspects of aging starting from a very young age.
- As there is no known cure, few people with progeria exceed their teens.



- A famous example of people with progeria syndrome was **Sam Berns**, an activist who helped raise awareness of the disease. He died at age 17.

Sam Berns
(1996-2014)

http://www.eigerbio.com/about-hutchinson-gilford-progeria-syndrome/
https://www.ted.com/talks/sam_berns_my_philosophy_for_a_happy_life?language=en

Hutchinson-Gilford progeria

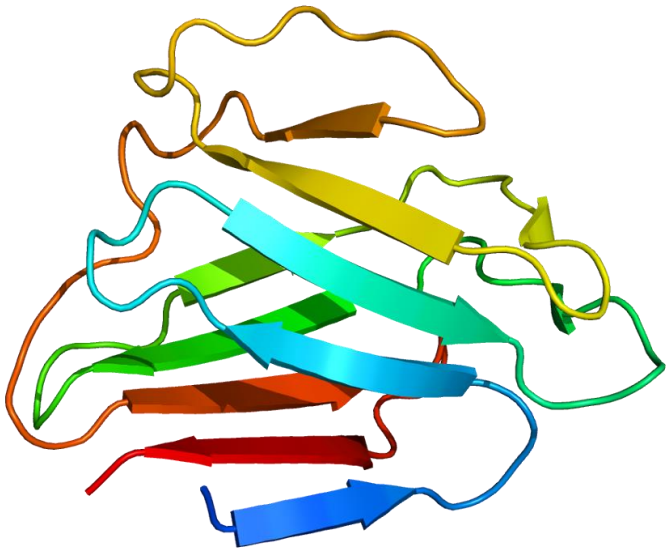
- The syndrome causes hair loss (alopecia), aged-looking skin, joint abnormalities, and a loss of fat under the skin. This condition does not affect intellectual development or the development of motor skills.

- People with Hutchinson-Gilford progeria syndrome experience severe hardening of the arteries (arteriosclerosis) beginning in childhood. This condition greatly increases the chances of having a heart attack or stroke at a young age, which causes their premature death in 90% of the cases.

https://ghr.nlm.nih.gov/condition/hutchinson-gilford-progeria-syndrome

Causes

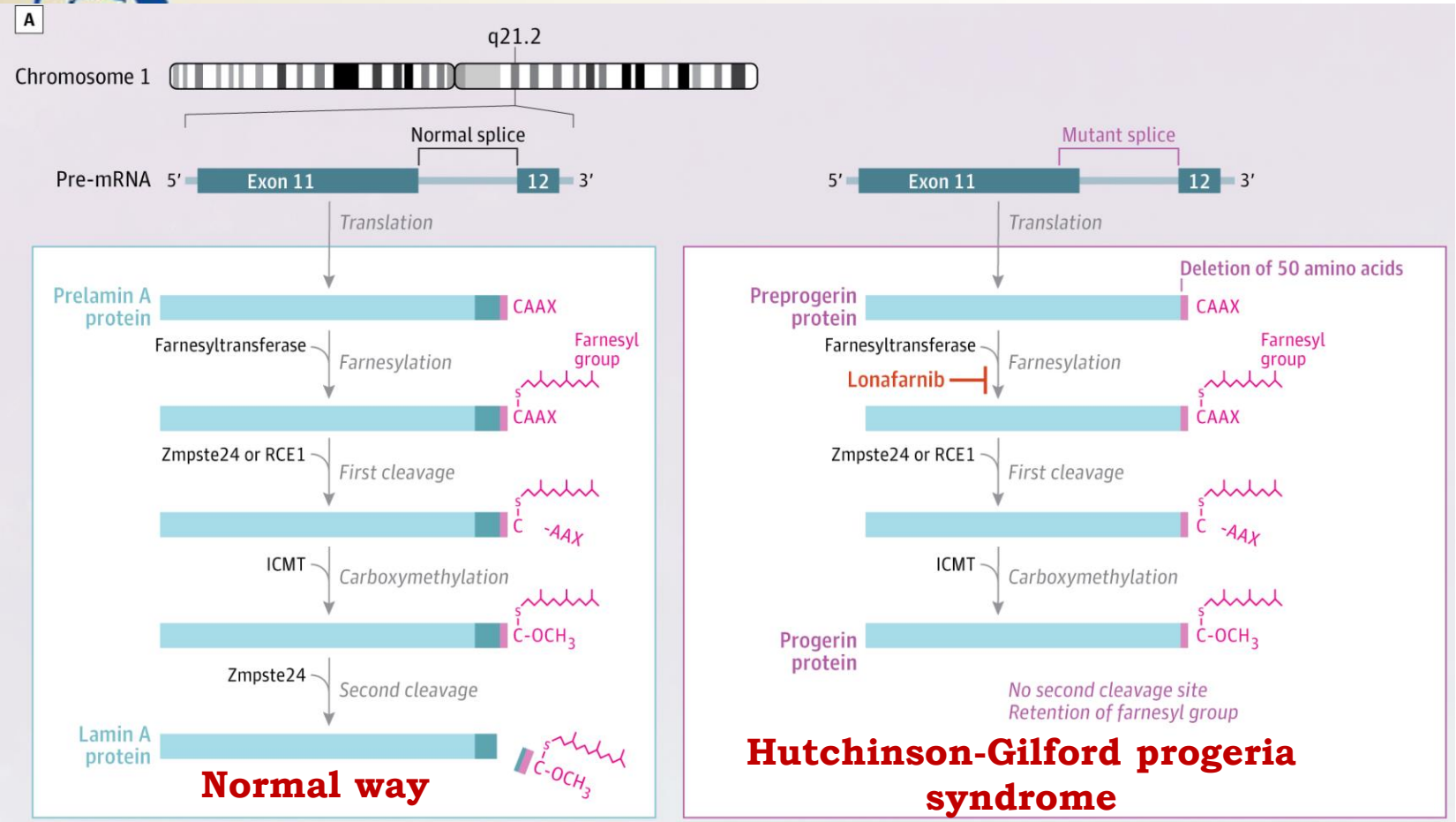
- Hutchinson-Gilford progeria syndrome (HGPS) is caused by mutations (changes) in the *LMNA* gene, which encodes Lamin A, a structural protein that helps to keep cells of the body strong and stable. People with Hutchinson-Gilford progeria syndrome have abnormal prelamin A (named Progerin), which causes damage to cells and leads to symptoms of aging early in life.



Lamin A

https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182118#key-facts-section

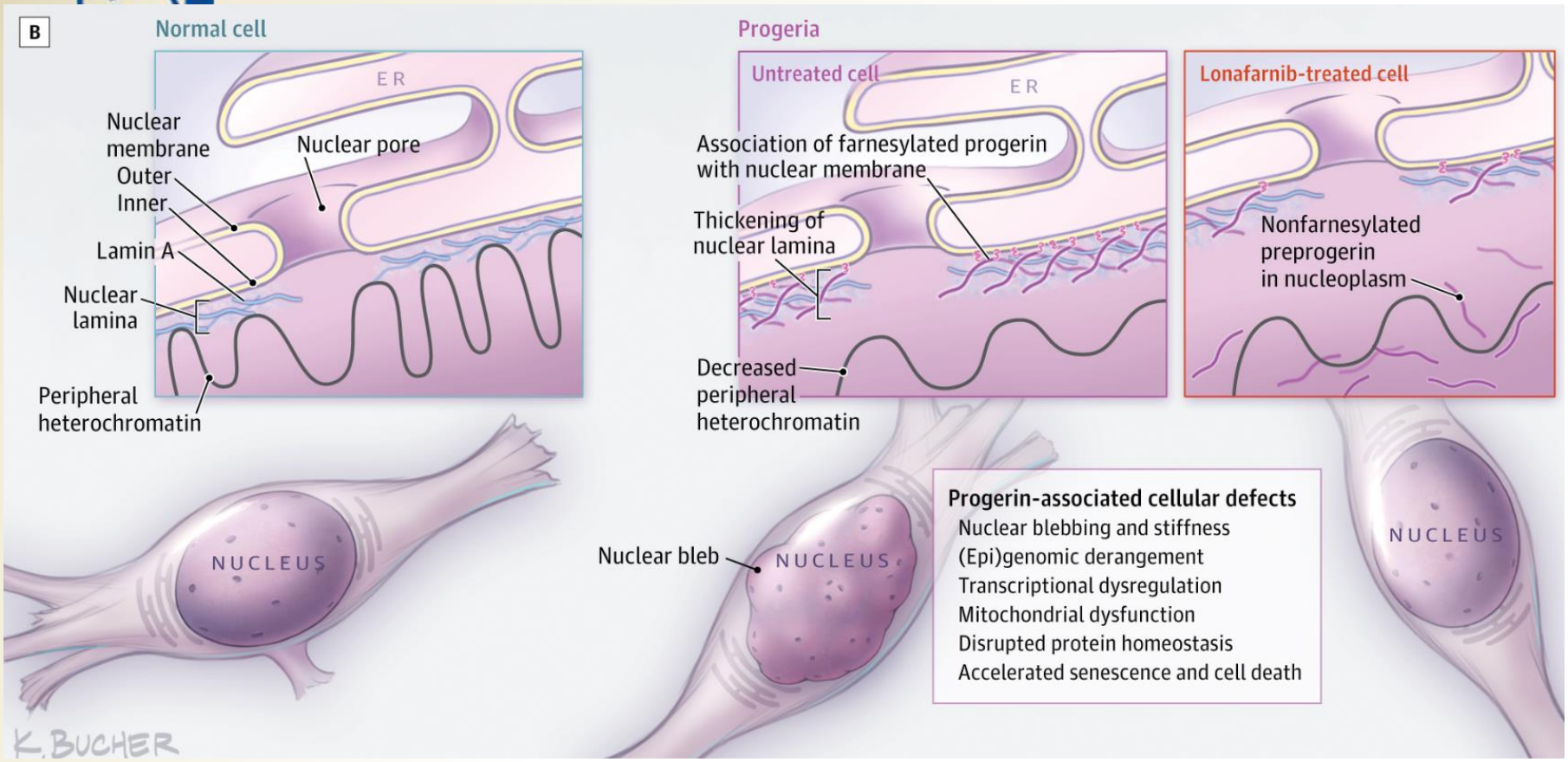
Causes



- The mutation on the LMNA gene causes the deletion of 50 amino acids, which results in a protein without a second cleavage, thus instead of Lamin A, Progerin is produced, which causes damage in the cell.
- Lonafarnib stops the mutant Progerin production before the farnesylation, resulting in harmless Preprogerin

Source: Gordon et al., JAMA, 319(16), p1687 (2018) doi:10.1001/jama.2018.3264

Causes



- The Lamin A is incorporated in inner wall of the nucleus in a normal cell. The mutant farnesylated Progerin intercalates into the inner nuclear membrane, where it accumulates and causes damage to the cell.
- Lonafarnib does not allow the Progerin production. The nonfarnesylated Preprogerin cannot accumulate in the nuclear membrane, thus keeps the cell healthier.

Source: Gordon et al., JAMA, 319(16), p1687 (2018) doi:10.1001/jama.2018.3264

Current status

- It is thought that Lonafarnib may help prevent formation of the mutant Progerin thereby improving symptoms of the disease.

- On 14 December 2018, **orphan designation** (EU/3/18/2118) was granted by the European Commission to Eiger Biopharmaceuticals Europe Limited, United Kingdom, for Lonafarnib for the treatment of Hutchinson-Gilford progeria syndrome.
- Breakthrough Therapy Designation and Rare Pediatric Disease Designation by the FDA.
- Trade name: **Zokinvy** for progeria/ **Sarasar** for Hepatitis Delta virus
- Other indications for lonafarnib: Hepatitis D, various types of cancer

https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182118#key-facts-section

http://www.eigerbio.com/eiger-initiates-rolling-submission-of-new-drug-application-nda-with-fda-for-lonafarnib-for-treatment-of-progeria-and-progeroid-laminopathies/

Current status

- Eiger Initiates Rolling Submission of New Drug Application (NDA) with FDA for Lonafarnib for Treatment of Progeria and Progeroid Laminopathies Rolling NDA Submission Planned for Completion in First Quarter 2020 Marketing Authorization Application (MAA) to EMA Planned in First Quarter 2020

http://www.eigerbio.com/category/hutchinson-gilford-progeria-syndrome/

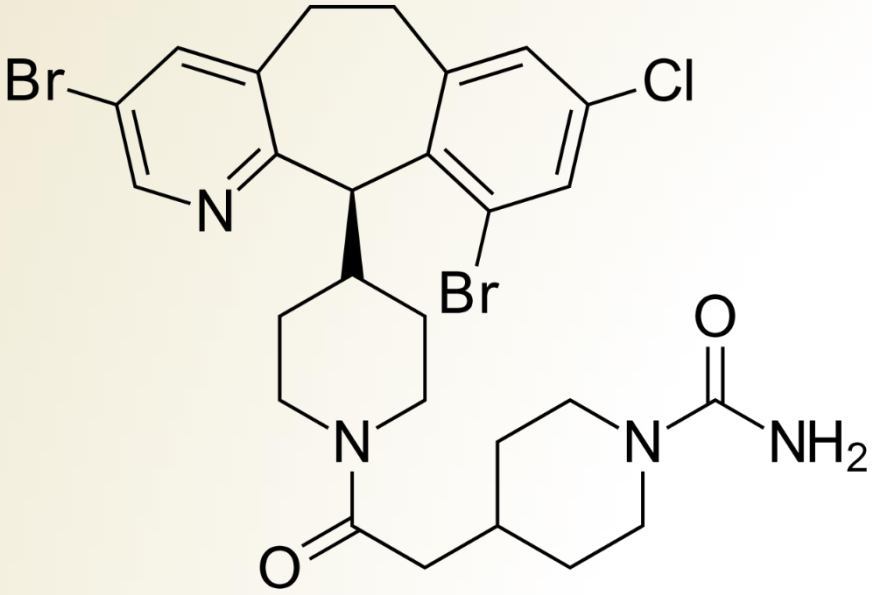
IP background

- **Concert Pharmaceuticals (2009)**
  Tricyclic benzo[S $_5$O]cyclohepta[I^-B]pyridine derivatives and uses thereof
  WO 2009/145852 A1 **Accepted in US, abandoned in 2014**
  The patent describing the structure of Lonafarnib for the first time

- **Eiger Biopharmaceuticals (2016)**
  Pharmaceutical compositions comprising Lonafarnib and Ritonavir
  WO 2016/172342 A1 **Patent pending in EU, USA**
  The PCT patent application for the Eiger formulation of Lonafarnib, combined with Ritonavir, since they are used together in Hepatitis Delta virus treatment

- **Cyclolab Ltd. (2019)**
  A new pharmaceutical formulation of Lonafarnib with a sulfobutylether β-cyclodextrin
  US 16685632 **Patent pending in USA**
  The PCT patent application for the Cyclolab technology

Structure of Lonafarnib



- Tricyclic (benzocycloheptapyridine) carboxamide derviative
- Water Solubility: 0.000829 mg/mL
- logP: 4-5
- Patients receive oral Lonafarnib either by **oral capsule** or by **liquid suspension** dispersed in Ora-Blend SF or Ora-Plus (Perrigan Company, Allegan, MI, USA)

Clinical study of Lonafarnib

- A prior publication: Ulrich et al., Neurology,81, p427 (2013)
- This article describes the results of the **Phase II** clinical trial for Hutchinson-Gilford progeria syndrome (HGPS)
- 25 patients received lonafarnib either by **capsule** or liquid **suspension** for the minimum of 2 years
- The formulation did not contain cyclodextrins
- The dose of Lonafarnib was between 115-150 mg/m^2, which is around 100-150 mg
- The study provided evidence that the lonafarnib therapy can improve the neurologic status of children with HGPS, reducing the prevalence of stroke and transient ischemic attacks (mini strokes) and also the prevalence and frequency of headaches.

Formulation of Lonafarnib with cyclodextrin

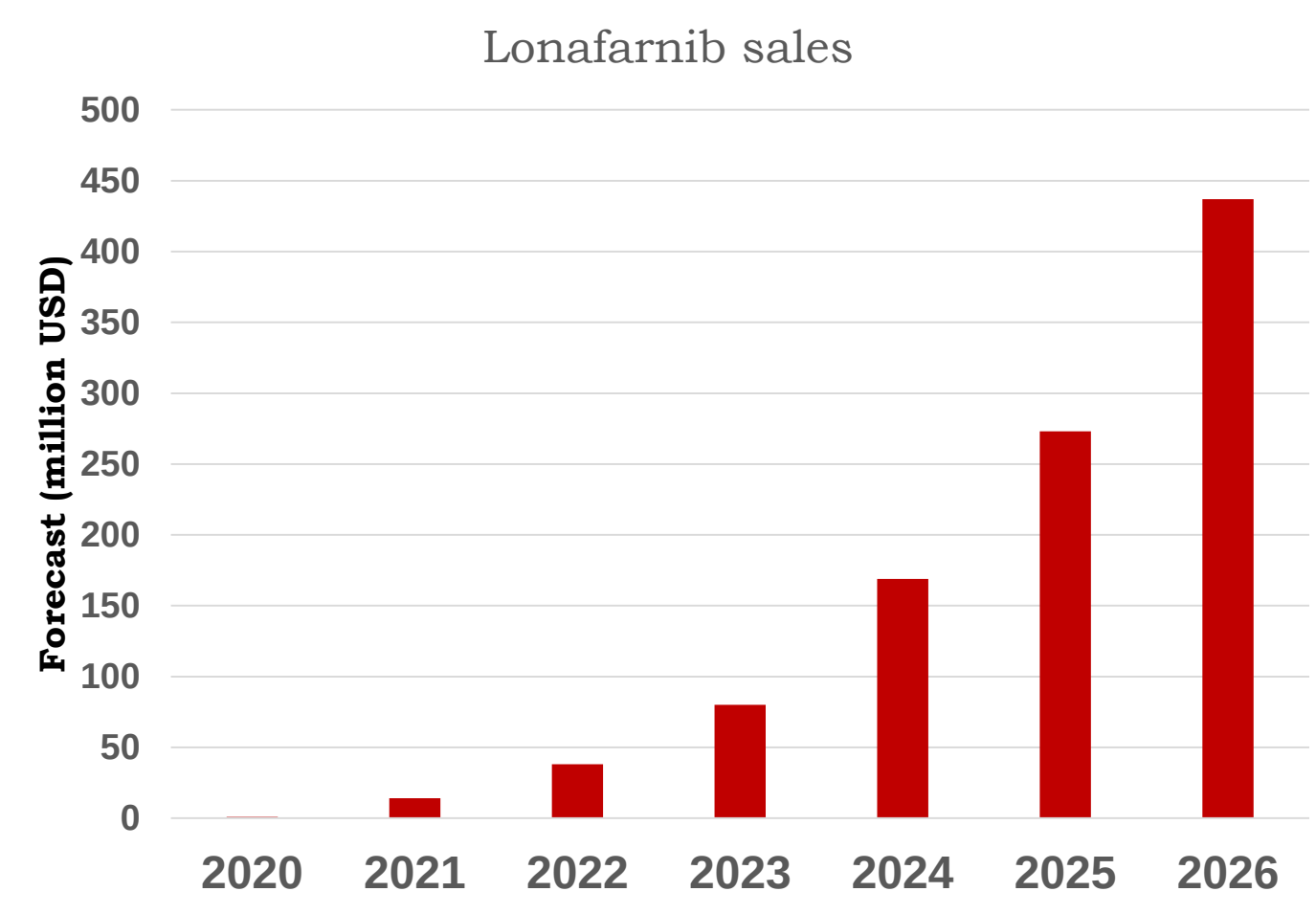
- A prior publication: Hernandez et al., Science Translational Medicine, 11, eaat3005 (2019)
- 20% of 2-hydroxypropyl beta cyclodextrin (HPBCD, hydroxypropyl betadex) was used
- Lonafarnib was dissolved first in DMSO, heated at 95°C until it became clear and then resuspended in 20% HPBCD
- A **suspension** of Lonafarnib was obtained for the (pre)clinically relevant concentration of the drug (12 mg/ml).

Cyclolab's procedure

- 12 mg/ml Lonafarnib **solution**
- moderately acidic pH
- moderately concentrated SBECD

- Since lonafarnib is in solution, this liquid formulation would allow **better bioavailability** than capsules or suspensions.
- The SBECD enabled Lonafarnib was **patented in 2019 by Cyclolab**

Market forecast



- This data potentially includes the sales forecasts mainly for the other use of Lonafarnib (Hepatitis D virus) for the Sarasar pruduct.

Source: Globaldata

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