Steps to registration of an oral treatment for sleeping sickness

SCIENTIFIC DAYS

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Background

Research into the treatment of sleeping sickness treatment was initiated by DND*i* at the request of MSF. Fexinidazole is the first new chemical entity brought by DND*i* through all stages of the drug development pipeline and into patients, including three clinical studies involving 749 patients. This 10 day all-oral treatment (1800 mg per day for 4 days followed by 1200 mg per day for 6 days) for both stages of *T. b. gambiense* sleeping sickness (g-HAT), is a significant improvement upon previous treatments because it eliminates the need for systematic hospitalization and should remove the need for systematic lumbar punctures.

Completed trials

	Trial population		Number of participants	Efficacy based on success rate	Serious TEAEs Subjects (%) [no. events]
*FEX004	Adults in-patients	Stage 2	264 (+130 NECT)	91.2% (97·06% CI −11·2 to −1·6; p=0·0029)	31 (12%) [51]
FEX005	Adults in-patients	Stage 1, early stage 2	230	98.7% (96.2-99.7%)	20 (9%) [32]
FEX006	Children ≥6-14 in-patients	All stages	125	97.6% (93.1-99.5%)	10 (8%) [14]

*Fexinidazole vs nifurtimox-eflornithine combination treatment (NECT, first-line therapy for late stage g-HAT) comparative non-inferiority pivotal study

Methods

For high-priority medicines and vaccines for use outside the EU that address unmet medical needs or are of major public health interest, the European Medicines Agency (EMA) has in place a regulatory pathway for review of these products, Article 58.

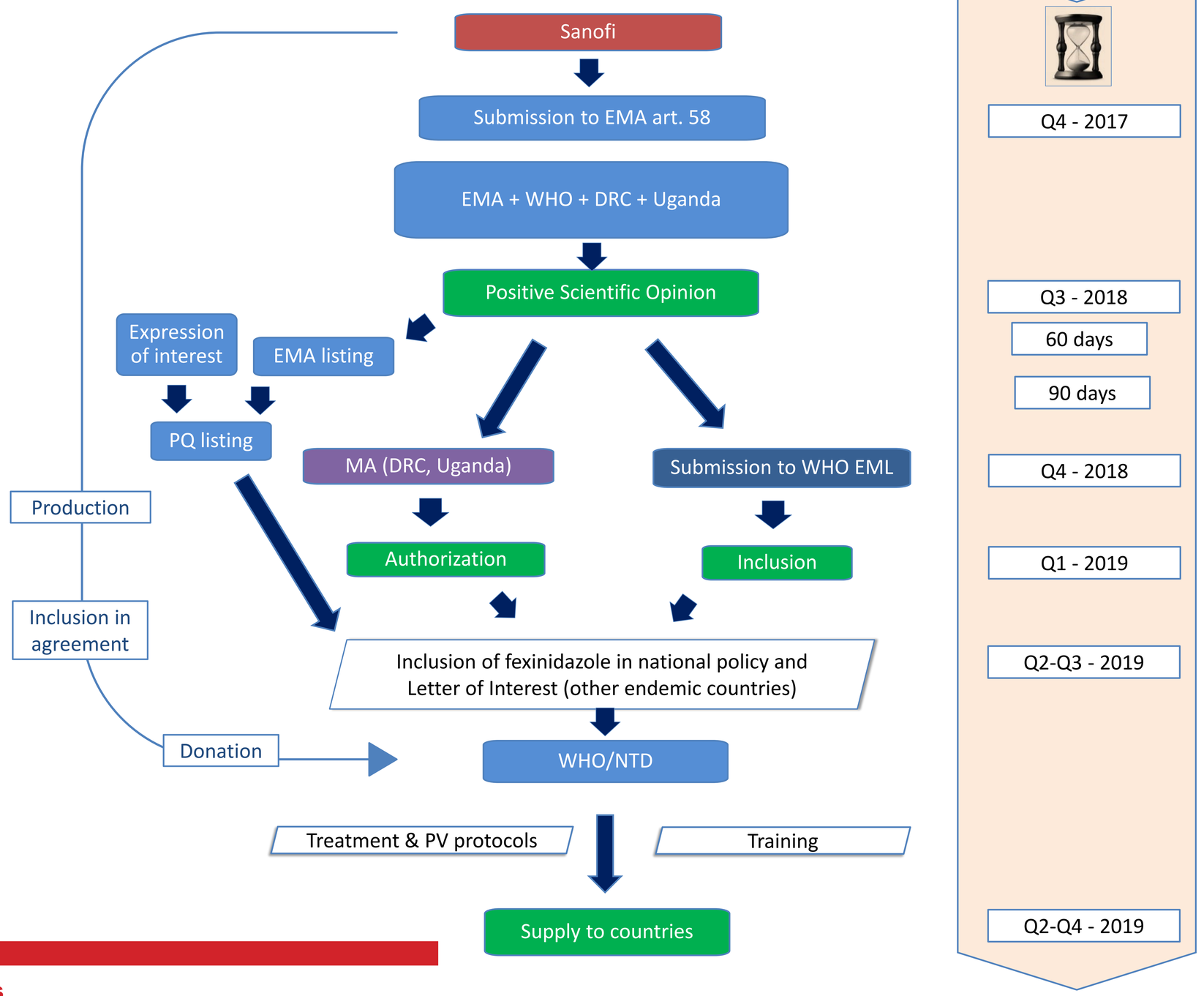
Article 58 is a regulatory process involving the EMA-CHMP (Committee for Medicinal Products for Human Use), the World Health Organization, and national regulators in target countries in evaluating medicines to the same standards as those marketed within the EU. In this case, the target countries were Democratic Republic of Congo and Uganda. Regulators, experts and observers from concerned endemic countries are invited to participate, to ensure that local knowledge and specific disease expertise is included in the scientific review.

Once the positive scientific opinion was granted by the EMA for fexinidazole, this process enabled national marketing authorisation or registration of a medicine at national level. WHO will develop guidelines for use; other endemic countries could then include fexinidazole into national policy and submit letters to WHO to request the product, which then facilitates supply to these countries.

In addition, fexinidazole was added to the prequalification list following the positive opinion and was submitted for inclusion in the WHO Essential Medicines List (EML).

Since fexinidazole is planned to be submitted to the FDA for registration, the DNDi team ran a mock GCP inspection in order to ensure full compliance with FDA regulatory requirements.

From research to treatment



Results

- December 2017: dossier submitted to the EMA
- November 2018: EMA adopted a positive scientific opinion of fexinidazole
- November 2018: submission to EML
- December 2018: fexinidazole registered in DRC.
- February 2019: added to the prequalification list

On-going & future trials

- FEX009 adults & children, all stages, in-and out-patients (including breastfeeding or pregnant women in the second or third trimester.)
- Phase II/III *T.b. rhodiense* HAT planned for mid-2019 in Malawi and Uganda.
- Phase IV in preparation in DRC, South Sudan, Guinea and Angola; and in CAR with MSF.

Conclusion

Due to the involvement of in-country experts and WHO in the EMA Article 58 review process, this innovative mechanism facilitated registration of fexinidazole in DRC in just 39 days, with registration in Uganda expected shortly.

Thanks to this regulatory process, which was based on data collected in patients recruited by MSF in DRC and CAR, and by the PNLTHA, new g-HAT patients should shortly benefit from this simplified, short-course oral regimen, the second transformative therapeutic improvement delivered by DNDi for sleeping sickness patients.

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Partners

DNDi Drugs for Neglected Diseases *initiative*

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