Armenia Experience:
Treatment Initiative of XDR and pre-XDR with Compassionate Use of Bedaqiline, Imipenem and linezolid

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Armenia: Rationale for CU

- **One of 27 high MDR-TB burden countries**
- **MDR estimates (NRL Armenia 2011)**
  - **18.7%** in new & **55.6%** in re-treatment cases
  - **9.0%** (6.7–11.2%) XDR in MDR-TB cases (Globally/WHO2012)
- **10-15%** DRTB patients fail treatment
- **Estimated 25-30 XDR(/Pre-XDR)TB patients were in desperate situation:**
  - approved treatment options have failed and/or no satisfactory therapy exists
  - life-threatening condition
  - Ongoing medical and social needs (e.g.palliative care, isolation)
  - no access to clinical trials

Challenges to Introduce CU in Armenia

- There was no legal framework for compassionate use in general
- MOH/NTP was not aware of what compassionate use meant for TB patients
- No previous use of other group 5 drugs for XDRTB treatments (other than Cfz, Amox-Clav and Clr)
- No use of Investigational New Drugs for other diseases (e.g., cancer, Alzheimer's , AIDS) when other treatment options are exhausted!

Timeline for the introduction of CU

- **October 2012:** NTP Armenia signed the 'Confidentiality Agreement' with Janssens
- **Nov 2012:** NTP formed an Ethic Committee to review bedaquiline use for TB patient
- **Jan 2013:** Ethic Committee and MOH approved Bedaquiline importation for humanitarian reasons (life saving treatment whilst CU legislation is in the process of development)
- **25th January:** first patient sent to MSF-PIH committee – first cases accross MSF and PIH
- **Feb 2013:** 1st case sent to Janssen
- **March 2013:** Janssen approved 1st 4 cases
- **April 2013:** Bedaquiline received (6-month drugs/patient)

Submission & Approval for CU

1. Treating doctors (MSF/MOH) select patients based on the **CU eligibility criteria**
2. Present the cases to the **DR TB Committee** for endorsement
3. Submit the cases to **MSF-PIH Medical Committee for** endorsement and clinical advices
    a. 7 members – 3 from MSF, 2 from PIH, 1 expert from Argentina and one from the Union (IUTLD)
    b. Patient identified only by number (confidentiality)
    c. If a disagreement, 2 external experts are consulted
4. Submit the patients clinical dossier to **Janssen** for the final approval
5. Obtain the written informed **consent** from the patients to be treated
6. Importation procedure (4-6 weeks)

Eligibility for CU access to new drugs

- In practice it is for patients failing or likely to fail treatment:
  - XDR
  - Pre-XDR (FQ)
  - MDR who have failed all treatment

- Age ≥ **18 yrs**
- Women of childbearing age**,** negative **pregnancy test**
- Criteria for caution
  - Laboratory abnormalites (renal and liver function)
  - Long QT interval or other ECG abnormalities
  - Family history of long QT syndrome

Consequences of CU Initiative…

- **Use of other group 5 drugs for XDRTB**
  - **Linezolid**
    - Side effects – haemotological, peripheral neuropathy
      - MOH and MSF doctors trained for the eary detection of the side effect and proper management of the minor reaction
    - Expensive – but now generic form is available (role of MSF pharamacist)
  - **Imipenem**
    - **Daily dosage 1g 2 time a days with 10-12 hours interval**
    - **Intravenus infusion for more then 2 months , even during full treatment**
    - **Solution :Port a Cat insertion , looking for other options close peripheral catheter**
    - **special ambulatory care/ hospitalization needs, no framework for the ambulatory care for the Imp**

Consequences of CU Initiative…

- **Enhanced pharmcovigilance and reporting of adverse events**
  - Serious Adverse Event (SAE) reporting within 24 hours!
- **Additional monitoring & reporting systems**
  - More comprehensive initial clinical assessment: a complete blood count, liver and renal function tests, lipase, and ECG, as well as clinical assessment of neuropathy etc
  - More frequent medical follow-up - daily for the first two weeks, then weekly for the first initial two months and in any emergency
  - Additional tests: ECG: weekly for the initial month, then monthly if no abnormal findings. If bdq is prescribed with FQ or Cfz or other drugs that may prolong QT, ECG should be done weekly throughout the treatment period
- Need to revive clinical skills that traditionally TB doctors/nurses do not practice (e.g, no-one knows how to read an ECG, IV drugs use, other monitoring)

TMC207 Compassionate Use Program TMC207TBC3002

02 October 2013

FPI	LPI	LPO
Mar - 11		

- Operated by GCO
- CU patient inclusion based on unsollicted request (countries not known up front)s in each country

Country	Patients approved	Pts received treatment	Expected Closure date (Marketing Auth. /reimbursement)
Argentina	1	1	*TBD**
Armenia	29	26	*TBD**
Austria	12	12	*TBD**
Bangladesh	5	5	*TBD**
Belgium	3	3	*TBD**
Botswana	4	4	*TBD**
Canada	2	2	*TBD**
Ethiopia	1	1	*TBD**
Estonia	1		*TBD**
France (ATU)	*71*	*71*	*TBD**
Georgia	6	5	*TBD**
Germany	15	15	*TBD**
Greece	1	1	*TBD**
India	8	8	*TBD**
Italy	5	5	*TBD**
Kazakhstan	9	-	*TBD**
Latvia	11	11	*TBD**
Lebanon	1	1	*TBD**
Moldova	1		*TBD**
Nepal	2	2	*TBD**
Netherlands	2	2	*TBD**
Niger	3	3	*TBD**
Nigeria	1	1	*TBD**
Papua New Guinea	1	1	*TBD**
Peru	1	1	*TBD**
Romania	1	1	*TBD**
South Africa	34	34	*TBD**
Sweden	3	3	*TBD**
Switserland	1	1	*TBD**
Taiwan	2	2	*TBD**
United Kingdom	10	10	*TBD**
United States of America	5	5	*TBD**
TOTAL	**254**	**237**	

* To Be Decided

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

GCO GLOBAL CLINICAL OPERATIONS

MEDICAL AFFAIRS

Timeline of Approval Process

	Average Days
Assessment & Tx initiation	52
MSF-PIH Committee review	11
J&J Assessment	16
Importation Procedures	28

Current Situation (23.11.2013)

Discussed with MSF-PIH	40
Patients started treatment	24
Patient approved but waiting for tx	3
Approved and refused treatment	4
Died during submission	1
Died before starting treatment	1
Pending approval with J&J	1
Rejected by J&J	2
Rejected by MSF-PIH	3
MSF-PIH approved but not sent to J&J as patient refused	1

Bacteriological Status

16 (67%) patients have achieved negative (sm/culture or both) bacteriological status thus far!

Smear/Culture or both Convention (n.16)				
	1st month	2nd month	3rd month	4th month
Number of patients	9	5	1	1
Proportion	56%	31%	6%	6%

Interim outcome/status (n.24)

24 Patients Started Tx	N (%)
Still on treatment	22(92)
Left for Russian (promised to come back in 2 week!?)	1(4)
Tx interruption /defaulted	0(0)
Short interruption due to Lzd or medical complication and resumed tx	3(13)
Bedaquiline course completed	4(17)
Severe Adverse Effect Reported to J&J	2(8)
Severe Adverse Effect related to Bedaquiline	0(0)
Failure	1(4)

Conclusion

- New drugs giving hope to desperate cases
- Opportunity to introduce other 5th line drugs (e.g, Ipm, Lzd)
- NTP/MOH is likely to extend access to new drugs!
- Major technical and operational challenges
- Many ongoing questions:
  - How best to use the drugs
  - How to avoid development of resistance.