Unit: Technical Assessment Unit

Public assessment report for biological products

(Elahere)

Administrative information:

Trade name of the medicinal product:	Elahere 5 mg/mL concentrate for solution for infusion
INN (or common name) of the active substance(s):	Mirvetuximab Soravtansine
Manufacturer of the finished product	BSP Pharmaceuticals - Italy
Marketing Authorization holder	AbbVie Deutschland GmbH - Germany
Applied Indication(s):	As a monotherapy for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.
Pharmaceutical form(s) and strength(s):	Liquid formulation for intravenous (IV) administration. Each mL of concentrate for solution for infusion contains 5 mg of mirvetuximab soravtansine. One vial contains 100 mg mirvetuximab soravtansine in 20 mL.
Route of administration	Intravenous infusion
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

ADC	Antibody-Drug Conjugate
ADA	Anti-drug antibody
AUC∞	area under the curve extrapolated to infinity
BICR	Blinded Independent Central Review
cDNA	Complementary DNA
Cmax	maximum plasma concentration
DM4	maytansinoid Ravtansine
DOR	Duration of response

EOC	epithelial ovarian cancer
ESMO	European Society for Medical Oncology
FOLR1	folate receptor 1
FRα	folate receptor alpha
GLP	good laboratory practice
hERG	Human ether-à-go-go-related gene)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC	investigator's choice
IgG1	immunoglobulin G1
IMGN853	Mirvetuximab soravtansine
IV	Intravenous
MTD	Maximum Tolerated Dose
NOAEL	No observed-adverse-effect-level
NAbs	Neutralizing antibodies
OS	Overall survival
PR	Partial response/remission
PK	Pharmacokinitics
PROC	Platinum-resistant ovarian cancer
QT	QT interval
QTc	Corrected QT interval
SAEs	Serious AEs
t½	Elimination half-life
TAb	Total antibody
DS	drug substance

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1. **Quality aspects:**

1.2.1 Introduction

The finished product is presented as a concentrate solution for infusion containing 5 mg/mL of mirvetuximab soravtansine as active substance.

Other ingredients are: glacial acetic acid, sodium acetate, sucrose, polysorbate 20 and water for injections.

The product is available in type I glass vial with a butyl rubber stopper and an aluminum seal with a royal blue polypropylene flip cap.

1.2.2 Drug Substance (Active ingredient):

- The mirvetuximab soravtansine active substance, also referred to as drug substance is an antibody-drug conjugate manufactured from 3 DS intermediates:
  - DM4 toxic payload
  - sulfo-SPDB linker
  - M9346A monoclonal antibody

- **Manufacturer:**
  BSP Pharmaceuticals -Italy

- **Stability of drug substance**
  -Drug Substance: 36 months ≤ -70°C.
  -Drug substance intermediate (DM4 toxic payload): 60 months ≤ -15 °C
  -Drug substance intermediate (M9346A antibody): 48 months ≤ -50 °C
  -Drug substance intermediate (Sulfo-SPDB): 60 months ≤ −60°C

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

- The Drug product is a 5.0 mg/mL solution. Each vial contains 100 mg of deliverable mirvetuximab soravtansine and the formulated composition as follows: 10 mM acetate, 9 % (w/v) sucrose, 0.01 % (w/v) polysorbate 20, and 5 mg/mL mirvetuximab soravtansine at pH 5.0. To ensure that 20 mL can be withdrawn from the vial, the target fill volume includes an overfill. The target fill is 21.1 mL per vial.
- **Manufacturer:**
  BSP Pharmaceuticals - Italy

- **Stability of the drug product.**
  Finished Product (un opened vial): 60 months
  Finished Product (un opened vial):
  -Store upright in a refrigerator (2 °C - 8 °C).
  -Do not freeze.

-Keep the vial in the outer carton in order to protect from light
-Do not shake the vial.
Diluted solution:
After dilution the chemical and physical stability has been demonstrated between 1 mg/mL and
2 mg/mL for 8 hours at 15 ˚C – 25 ˚C or for 24 hours at 2 – 8 ˚C followed by 8 hours at
15 – 25 ˚C.

2. Non–clinical aspect

Ovarian cancer is a lethal disease with 313,959 new cases and 207,252 deaths reported worldwide in 2020. The incidence of ovarian cancer is increasing globally with a projected 450,000 cases by 2040. Ovarian cancer is the fifth leading cause of cancer death in women in the United States. In 2022, 19,880 new cases and 12,810 deaths were anticipated. In the European Union, ovarian cancer is estimated to account for 26,500 deaths annually.

According to current ESMO guidelines, epithelial ovarian cancer (EOC) represents a heterogeneous spectrum of disease entities at a clinical, pathological and molecular level. Ovarian cancer is the second most lethal gynaecological malignancy worldwide, behind cervical cancer and the first in developed countries. There is currently no reliable screening method for ovarian cancer.

Mirvetuximab soravtansine (also known as IMGN853) is an antibody-drug conjugate (ADC) that binds with high specificity and affinity to folate receptor alpha (FRα, also referred to as folate receptor 1 [FOLR1]), a glycosylphosphatidylinositol-linked protein. FRα has limited normal tissue expression and high expression in several solid tumors, especially serous epithelial ovarian cancer. Mirvetuximab soravtansine consists of an anti-FRα monoclonal antibody (immunoglobulin G1 [IgG1]) attached via a cleavable linker to the cytotoxic maytansinoid, DM4. Maytansinoids are anti-mitotic agents that inhibit tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis.

Upon binding to FRα, mirvetuximab soravtansine is internalized, followed by intracellular release of DM4 via proteolytic cleavage. DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death.

Pharmacology:

- The nonclinical testing program of mirvetuximab soravtansine was designed in consideration of the ICH S9 Guideline.
- The functional activity and mechanism of action of mirvetuximab soravtansine were elucidated in multiple in vitro and in vivo studies. In vitro studies have demonstrated that mirvetuximab soravtansine binds cell surface FRα with high apparent affinity and showed potent and selective cytotoxicity against FRα-expressing tumor cells. In addition, In vitro cytotoxicity studies demonstrated a positive correlation between

the level of FRα expression, the amount of catabolites generated, and the sensitivity of cells to mirvetuximab soravtansine.
- In ovarian cancer xenograft models, mirvetuximab soravtansine activity was dependent on the level of FRα expression; those models with higher FRα expression had partial and complete remission when treated with mirvetuximab soravtansine, as opposed to those with lower FRα where little antitumor activity was observed.
- Regarding to cardiac risk assessment, the hERG channel studies suggest a low likelihood of DM4 or its metabolite S-methyl DM4 interaction with the hERG channel. Finally, a repeat dose, GLP-toxicity study in cynomolgus monkeys identified no changes attributed to mirvetuximab soravtansine in QT/QTc interval, PR interval, QRS duration, RR interval, or heart rate.
- Stand-alone secondary pharmacodynamic studies were not conducted. Potential, off-target, platform toxicology effects of mirvetuximab soravtansine were explored in payload toxicology studies.
- Pharmacodynamic drug interactions for this receptor are unexpected since Mirvetuximab soravtansine is a drug that specifically targets the alpha folate receptor, and no other drugs are available against the same receptor.

Pharmacokinetics:
- No dedicated absorption studies were conducted since Mirvetuximab soravtansine is an intravenous drug. The absorption is considered complete (100%). In both monkeys and rabbits, maximal concentrations for ADC and TAb were observed immediately following post infusion, and both C_{max} and AUC_{∞} generally increased proportionally with dose. The mean Day 64 AUC_{∞} across both males and females at the no observed-adverse-effect-level (NOAEL) of 4 mg/kg. In monkeys, the ADC mean $t_{½}$ across males and females ranged from 97.4 to 103 hours following single doses and from 105 to 121 hours with repeated administrations. The observed $t_{½}$ for Tab was approximately 1.5 to 2-fold longer than that observed for ADC. Thus, TAb exposures were consistently higher relative to ADC.
- DM4, and the active metabolite, S-methyl DM4, were highly protein bound in human and rat (>99%) plasma. In monkey plasma, DM4 was >99% bound, and S-methyl DM4 was 96% bound. A radiolabeled distribution study was conducted in Dutch Belted rabbits to assess distribution in the ocular tissues. Radioactivity was detected in plasma and all ocular tissues; the elimination was slow with half-lives ranging from 70 to 120 hours. A study was conducted in rats to characterize the disposition of radiolabeled mirvetuximab soravtansine following a single IV administration. The highest radioactivity was observed in the liver, lung, and kidney in addition to bone marrow and the spleen. Radioactivity was detected in the eyes and testes, with concentrations in the eye being maintained through 336 hours postdose, indicating a slow clearance of radioactivity from this tissue.
- An in vitro study with human hepatic microsomes and cDNA-derived CYP450s showed CYP-mediated metabolism, predominantly via CYP3A4 for both DM4 and S-methyl DM4.
- The proposed metabolic pathway for radiolabelled mirvetuximab soravtansine in rats includes the identification of 5 metabolites. DM4 and S-methyl DM4 were the only primary plasma metabolites. Fecal excretion was the predominant route of elimination.

Toxicology:

- The cynomolgus monkey was identified as the most appropriate animal species for toxicological evaluation of mirvetuximab soravtansine. The toxicity of mirvetuximab soravtansine was assessed following single and repeated IV administrations in the cynomolgus monkey. Ocular evaluations were performed in male Dutch Belted rabbits in repeat IV administration studies. The small molecule payload, DM4 was assessed in single dose toxicity studies in the mouse and cynomolgus monkey. Adverse effects identified were limited to skin and cellular depletion of the bone marrow and lymphoid tissues. Upon repeated exposure to mirvetuximab soravtansine, ocular findings became apparent in the corneal epithelium in both monkeys and rabbits. The toxicity profile of mirvetuximab soravtansine was similar to that of DM4 alone, indicating the toxicities identified were driven by the cytotoxic payload.
- In addition, DM4, and the metabolite, S-methyl DM4, were assessed in vitro for genotoxicity potential in a bacterial reverse mutation assay and in vivo in Sprague Dawley rats to assess clastogenicity. The in vitro genotoxicity assessment utilizing the bacterial reverse mutation assay was negative for DM4 and S-methyl DM4. However, both DM4 and S-methyl DM4 were positive in the rat bone marrow micronucleus assay. This is consistent with the pharmacological mechanism of action of mirvetuximab soravtansine.
- No carcinogenicity studies were conducted, as per ICH S9, carcinogenicity studies are not required for therapeutics intended to treat patients with advanced cancer.
- No reproductive or developmental studies were conducted. As per ICH S9, reproductive or developmental toxicity studies are not considered essential for drugs intended to treat patients with advanced cancers. The payload of mirvetuximab soravtansine, DM4 (S-methyl DM4), is cytotoxic, targets rapidly dividing cells, is clastogenic, and belongs to a class of compounds (maytansinoid) that has been well characterized as causing developmental toxicity. Moreover, the absence of juvenile toxicity study is acceptable for this product as it is indicated in adult patients only.

Overall conclusion: From the non-clinical point of view, no issues for concern regarding the data submitted for mirvetuximab soravtansine.

3. Clinical aspect:

Elahere (mirvetuximab soravtansine) is an antibody-drug conjugate (ADC) composed of a humanized IgG1 monoclonal antibody targeting folate receptor-alpha (FRα) conjugated to the cytotoxic maytansinoid DM4 via a cleavable disulfide linker. Upon binding to FRα-expressing tumor cells, the ADC is internalized, and DM4 is released intracellularly, disrupting microtubules, inducing cell cycle arrest and apoptosis.

The clinical development program includes:

Study Code	Phase	Design & Objective	Patient Population	Key Notes
IMGN853-0401	I	First-in-human, dose-escalation and expansion	FRα-positive solid tumors, relapsed/refractory	Determine MTD and RP2D; assess preliminary antitumor activity

Study Code	Phase	Design & Objective	Patient Population	Key Notes
IMGN853-0416 (MIRASOL)	III	Randomized, open-label vs. investigator's choice (IC) chemotherapy	Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer with high FRα	Pivotal efficacy study
IMGN853-0403	III	Randomized, open-label vs. IC chemotherapy	PROC with mixed FRα expression	Supportive Phase III study
IMGN853-0417	III	Single-arm pivotal study	Platinum-resistant high-grade FRα-positive ovarian cancer	Supportive efficacy study

Indication: Monotherapy for adult patients with FRα-positive, platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1–3 prior systemic therapies.

- **Clinical Efficacy & Immunogenicity**

IMGN853-0416 (MIRASOL):
Primary endpoint: Progression-free survival (PFSINV) HR = 0.65; median 5.62 vs. 3.98 months vs. IC chemotherapy.
Overall survival (OS) benefit: median OS 16.46 months vs. 12.75 months (Δ = 3.71 months).
Subgroup analyses (BEV-naive and BEV-pretreated) consistent with overall findings.
IMGN853-0417 (Single-arm study):
Confirmed ORR: 32.4% (investigator) and 31.6% (BICR).
Median duration of response (DOR): 5.9 months.
Median PFS: 4.3 months; 12-month OS not reached (31% mortality at median follow-up of 8.5 months).
IMGN853-0401 (Phase I Expansion Cohort):
Subgroup of PROC with high FRα: ORR 44%, median DOR 7.8 months, median PFS 6.7 months.
IMGN853-0403:
FRα-high subgroup: median PFS 4.8 months vs. 3.3 months IC chemotherapy; overall ITT: 4.1 vs. 4.4 months.
Immunogenicity:
Across 663 patients:
Pre-existing ADAs: 9%
Treatment-emergent ADAs: 8%
Treatment-enhanced ADAs: <1%
Neutralizing antibodies (NAbs): 5%
No meaningful impact of ADAs or NAbs on PK, efficacy, or safety was observed.
IRR risk in ADA-positive patients was low and manageable.

❖ **Clinical Safety**

Adverse Events (AEs):

Most AEs were Grade 1–2 and reversible; common events included ocular toxicity (blurred vision 43%, keratopathy 29%), GI disorders (nausea 40%, diarrhea 31%), fatigue (30%), and peripheral neuropathy (27%).

Pneumonitis occurred in 10%, mostly ≤ Grade 2; Grade 3–4 events <1%.

Hematologic toxicity was less than IC chemotherapy: neutropenia (<1%), anemia (<1%), thrombocytopenia (<1%).

TEAEs led to dose modification in 50% and permanent discontinuation in 12%.

Serious AEs (SAEs):

Related SAEs were infrequent (11%), primarily pneumonitis (4%).

Fatal TEAEs occurred in <1% and were mostly related to disease progression.

Special Safety Considerations:

Ocular toxicity managed with steroid eye drops and dose modifications.

Infusion-related reactions (<1% Grade 3) were rare and manageable.

Immunogenicity did not compromise safety.

❖ **Overall Conclusion**

Elahere demonstrates clinically meaningful efficacy as monotherapy for adult patients with FRα-positive, platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1-3 prior systemic regimens.

Safety profile is manageable with monitoring, dose adjustments, and supportive care.

Immunogenicity is low, with no apparent effect on PK, efficacy, or safety.

❖ **Benefit–Risk Conclusion**

The overall benefit-risk profile of Elahere (mirvetuximab soravtansine) is favorable for adult patients with FRα-positive, platinum-resistant high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who have received 1-3 prior systemic therapies. Clinical evidence from the pivotal MIRASOL study (IMGN853-0416), supported by Study 0417 and additional data, demonstrates improvements in progression-free and overall survival, alongside a manageable safety profile. Risk mitigation measures for ocular toxicity, pneumonitis, and infusion-related reactions are consistent with EMA-approved SmPC recommendations, and no further measures are deemed necessary.

4. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

EPAR: https://www.ema.europa.eu/en/documents/assessment-report/elahere-epar-public-assessment-report_en.pdf